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## CONTENTS

PAGE

Hypertensive and Ischaemic Heart Disease. By C. V. HARRISON AND PAUL WOOD . . . . . 205

Sino-Auricular Block, Interference Dissociation, and Different Recovery Rates of Excitation in the Bundle Branches. By HOWARD B. BURCHELL . . . . . 230

Electrocardiographic Studies in Cretins. By BERNARD SCHLEININGER AND BERNARD LANGDON . . . . . 237

The Effects of Thiocyanate on Basal and Supplemental Blood Pressures. By K. SEVERIN AUSTAD . . . . . 249

Radiokymography in Pulmonic Diseases and Tuberculosis. By K. SHIRLEY SMITH AND FRANKLIN G. WOOD . . . . . 257

Mass Miniature Radiography in the Detection of Heart Disease. By ALEX MACLEAN AND ALFRED ROGIN . . . . . 264

The Electrocardiogram of Posterior Cardiac Infarction. By PETER MEYER . . . . . 271

Transposition of the Aorta and Pulmonary Artery Demonstrated by Angiocardiography. By J. F. GOODWIN, R. STEINER, AND E. J. WAYNE . . . . . 279

The Results of Medical and Surgical Treatment of Essential Hypertension. By MARJORY A. KEITH, BARNET WOOLF, AND A. RAE GOLDIST . . . . . 287

European Cardiological Society . . . . . 295

Abstracts of Cardiology . . . . . 295

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# HYPERTENSIVE AND ISCHÆMIC HEART DISEASE:
## A COMPARATIVE CLINICAL AND PATHOLOGICAL STUDY

BY

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Hypertension and coronary sclerosis have been the subject of extensive study, yet they have many aspects that are still poorly understood. In the present work we have tried to ascertain how far they are dissociated and how far they overlap, and in particular we have studied their effects on the circulatory capacity of the coronary tree by injection and radiography.

Over a period of four years, from 1935 to 1939, we made a careful clinical study of most of the cases of ischæmic and hypertensive heart disease admitted to the wards of the Hammersmith Hospital. A total of 189 cases was analysed, of which 55 per cent were hypertensive, 30 per cent were ischæmic, and 15 per cent were mixed. Sooner or later some of these cases came to autopsy and so provided our chief material.

Each patient was classified in an arbitrary fashion, on clinical grounds, before the necropsy was made: those with angina pectoris or with myocardial infarction being considered to have ischæmic heart disease whatever the level of the blood pressure; those with high blood pressure and without angina or myocardial infarction being considered to have hypertensive heart disease.

The diagnosis of angina pectoris was made entirely on the history; that of myocardial infarction rested on well-known electrocardiographic criteria. Only patients with systolic blood pressures over 200 mm. and diastolic blood pressures over 100 mm., known to have been persistent, were included in the hypertensive series. In all there were twenty-seven hypertensive and fifteen ischæmic cases. In addition, twelve normal hearts were included in the pathological study to serve as controls.

In the hope of learning something about the factors governing cardiac enlargement, and in order to facilitate correlation between the clinical and pathological findings, an attempt was made to divide the cases into subgroups. Subdivision of the fifteen ischæmic cases proved too difficult, however, and was finally abandoned in favour of Table I; for it was not clear whether a profitable subdivision should be based on the height of the blood pressure, on the duration of myocardial ischæmia, or on the duration of heart failure; moreover, the blood pressure was not known prior to myocardial infarction in some instances.

The twenty-seven hypertensive cases, which followed a simpler course, were subdivided according to their stage of development when death intervened as follows.

(1) No cardiac symptoms: Cases 24, 47, 60, and 69. Death was from pulmonary embolism in Case 24, from cerebral hæmorrhage in Case 47, and from uræmia in Cases 60 and 69.

(2) Effort dyspnœa only: Cases 23, 36, 39, 43, 44, and 65. Death was from cerebral hæmorrhage in Cases 23 and 44, from herniotomy in Cases 36 and 39, from pneumonia in Case 43, and from hæmatemesis from peptic ulcer in Case 65.

(3) Left ventricular failure: Cases 11, 13, 19, 41, 45, and 68. Death was from cerebral hæmorrhage in Case 11, from uræmia in Cases 13, 19, 41, and 45, and from bronchopneumonia in Case 68.

(4) Full course—death in congestive heart failure: Cases 8, 32, 38, 58, 62, and 63 followed previous manifestations of left ventricular failure; Cases 28, 48, 49, 50, and 53 had no such previous manifestations.

### Clinical Features

Owing to the arbitrary nature of the clinical grouping, the complaint was necessarily one of pain in those with ischæmic heart disease: in ten it was the presenting feature, but in five it was less evident than dyspnœa. For the same reason pain was not present in the hypertensive group, except in an

TABLE I
ISCHÆMIC CASES

| Case No. | B.P. | Duration of angina (months) | Duration of myocardial infarction (months) | Duration of L.V. failure (months) | Duration of congestive heart failure (months) | Weight of patient |
|---|---|---|---|---|---|---|
| 17 | − | nil | <1 | <1 | nil | 12 st. 6 lb. |
| 22 | + | 24 | 24 | 24 | nil | 6 st. 7 lb. |
| 25 | − | 24 | 10 | nil | nil | — |
| 29 | + | 30 | <1 | nil | nil | — |
| 30 | + | nil | 20 | 18 | 1·5 | 8 st. 7 lb. |
| 37 | − | 1 | 1·5 | 2·5 | 2·5 | — |
| 40 | − | nil | 9 | 8 | nil | 13 st. 1 lb. |
| 42 | ++ | 18 | nil | nil | nil | 9 st. 4 lb. |
| 46 | + | 24 | 15 | terminal | terminal | 10 st. 0 lb. |
| 51 | + | nil | <1 | terminal | terminal | 12 st. 6 lb. |
| 52 | − | 24 | 24 | 3 | 3 | 10 st. 2 lb. |
| 55 | +++ | 12 | nil | 36 | terminal | 12 st. 9 lb. |
| 66 | − | 60 | <1 | <1 | terminal | 11 st. 0 lb. |
| 70 | − | 12 | <1 | <1 | <1 | — |
| 73 | + | 6 | 1 | 1 | 1 | — |

Note.—The blood pressure is recorded as + when it was in the region of 160–180/80–100 at its highest. In Case 42 it was higher than this, but only for a short time; Case 55 was originally classed as hypertensive, but had to be transferred to the ischæmic group owing to the development of angina. Case 37 was complicated by rheumatic heart disease with organic mitral incompetence.

atypical form which will be described later, but dyspnœa was invariable in those with cardiac symptoms.

There was a high incidence of rheumatic fever in both groups, four out of fifteen with ischæmic heart disease, and six out of twenty-seven with hypertensive heart disease. In two of each group the first attack had been in childhood, but in the remainder it had occurred in the third and fourth decades, and from the description might well have been rheumatoid arthritis. There was nothing else of significance in the previous history.

*Personal and family history.* The back-ground of these patients—their environment in childhood and later life, their private lives, their occupations, their relaxations, their habits and their reactions to the world in which they lived—seemed ordinary.

Cardiovascular disease was described in one or other or both parents in four of the ischæmic and in three of the hypertensive patients; but its exact nature, whether ischæmic or hypertensive, could not be ascertained.

*Sex and age.* There were twice as many males as females in the ischæmic group, whereas the proportion was equal in the hypertensive group. This difference is significant and well known. It was even more conspicuous in the larger clinical series. The sex distribution of the mixed cases was the same as of those with hypertension.

In the ischæmic group the average age for the men was 57 and for the women 68; in the hypertensive group the figures were 59 and 55 respectively. The point of interest is the older age of women with ischæmic heart disease. This, too, is now well known.

*Duration and onset.* The average duration of life from the onset of cardiac symptoms was 1·9 years for those with ischæmic heart disease, and 2·2 years for those with hypertensive heart disease. Since the period during which these investigations were carried out was only about four years, and since only those cases that died were included in the series, these figures do not indicate the true prognosis of the diseases in question.

Seven of the ischæmic cases began with angina pectoris, four with dyspnœa on exertion. Of those with dyspnœa, one had rheumatic heart disease and another had hypertensive heart disease as well as occlusive coronary atherosclerosis. Thus only two of those with pure ischæmic heart disease started their symptoms with dyspnœa.

In the hypertensive group, on the other hand, seventeen out of twenty-three with cardiac symptoms complained first of breathlessness; the initial symptom was fatigue in four of the remainder, and dropsy in the other two.

*Course.* Six ischæmic patients recovered sufficiently after the onset of cardiac symptoms to resume work without distress. The duration of this improvement was six months to two years. The work undertaken was not light, and one of them worked as a navvy for a year after his first myocardial

infarction. Thirteen out of the fifteen ischæmic cases developed myocardial infarction sooner or later; the two that died without this development were complicated, one by polycythæmia vera, the other by hypertensive heart disease. Six patients had paroxysmal cardiac dyspnœa following myocardial infarction, and five of these later developed systemic congestion. Two others had heart failure with systemic congestion without evidence of preceding left ventricular failure.

In the hypertensive group recovery of function was rare after the onset of cardiac symptoms, and was observed in only two out of twenty-three patients. Both experienced acute pulmonary œdema on unaccustomed effort, and subsequently recovered to the extent that they remained free from all symptoms for several months, even though they carried out their normal duties. In the remainder the condition steadily deteriorated.

The full course of hypertensive heart disease was witnessed in six patients: effort dyspnœa progressed to left ventricular failure at rest, and this was followed by failure with systemic congestion. The average duration of life after cardiac symptoms appeared was two years and one month, the range being six to forty-eight months.

Five cases gave no history of orthopnœa or paroxysmal cardiac dyspnœa, but after a period of effort dyspnœa developed heart failure with systemic congestion. Occasionally, the initial symptom was dropsy. The average duration of life from the onset of cardiac symptoms was two years and five months in this group, the range being six to eighty-four months.

Six patients died from non-cardiac causes at the stage of left ventricular failure—four from uræmia, one from cerebral hæmorrhage, and one from bronchopneumonia. The duration of cardiac symptoms in this group was twelve months (1 to 24 months).

Six patients died from non-cardiac causes at the stage of effort dyspnœa—two from cerebral hæmorrhage, two following herniotomy, one from pneumonia, and one from hæmatemesis due to peptic ulcer. The average duration of cardiac symptoms was two years and three months (1 to 84 months).

The remaining four cases had no cardiac symptoms. Two died with uræmia, one from cerebral hæmorrhage, and one from pulmonary embolism.

Thus the courses of ischæmic and hypertensive heart disease were similar in that left ventricular failure usually preceded failure with systemic congestion; they were dissimilar in that temporary recovery of function followed the onset of cardiac symptoms in about a third of the ischæmic cases, whereas steady deterioration characterized those with hypertension. It is interesting and important that only one patient initially classed as hypertensive was transferred later to the ischæmic group because of the development of angina pectoris or myocardial infarction.

### Incidents in the Course of Hypertensive Heart Disease

During the course of hypertensive heart disease certain events were observed that deserve special comment, for their significance was clinically obscure. Pathological studies clarified some of them.

*Case* 8. At one stage this man was severely constipated, and developed atypical chest pain followed by a lower blood pressure than usual, by a weaker cardiac impulse, and by left ventricular failure. The electrocardiogram showed low voltage QRS complexes and flat T waves in all leads. At necropsy, the heart showed marked left ventricular hypertrophy and weighed 695 g. In the skiagrams the coronary arteries appeared to be slightly smaller than those seen in other hypertensive hearts of similar weight, and their outlines were rather irregular; there were, however, no points of severe narrowing. The cardiac muscle showed patchy fibrosis at the base of the left ventricle posteriorly. The attack may have been due to temporary coronary insufficiency (Master *et al.*, 1947).

*Case* 19. For two years in this case there was frequent complaint of an ache behind the right shoulder, aggravated by exertion, and sometimes accompanied by a dull heavy ache in both arms. Latterly it was never mentioned. At autopsy, the left ventricle was hypertrophied and the heart weighed 480 g. Skiagrams showed coronary arteries of good size and with smooth outlines. There was no evidence of coronary narrowing nor of myocardial damage. It is concluded that the pain was not ischæmic.

*Case* 24. Six weeks before death this woman was seized with substernal pain, accompanied by pallor, sweating, cold skin, marked drop in blood pressure, and slight hæmoptysis. Serial cardiograms revealed the characteristic pattern of massive pulmonary embolism. The heart weighed only 340 g. The coronary arteries were larger than normal. There was no sign of coronary narrowing or myocardial damage. The presence of a relatively recent massive pulmonary embolism was confirmed.

*Case* 51. This man's symptoms began with acute pulmonary œdema after climbing some stairs. He was admitted with the diagnosis of acute myocardial infarction; but there was no convincing evidence of this. Cardiograms, however, were not obtained. The heart weighed 495 g. Skiagrams showed the coronary arteries to be narrowed with irregular

outlines. There was complete occlusion of the right recurrent branch, and a recent infarct at the base of the left ventricle posteriorly. The original diagnosis was correct and subsequent clinical judgment at fault.

*Case* 38. While in hospital this patient had an attack of severe substernal pain. Pallor and coldness of the skin were associated, and pericardial friction was heard later. But the blood pressure did not alter, and there were no electrocardiographic changes. The heart weighed 738 g. There was an organizing fibrinous pericarditis. Skiagrams showed the coronary arteries to be large with smooth outlines. There was no narrowing and no myocardial damage. Pericarditis was responsible for the pain.

*Case* 53. This woman had severe attacks of paroxysmal cardiac dyspnœa associated with syncope and substernal pain or choking. She also had attacks of left breast pain which radiated down the left arm and lasted two days. When the venous pressure was high she complained of præcordial tightness; this was twice relieved by venesection. The heart weighed 555 g. Skiagrams showed coronary arteries of good size with smooth outlines. There was no narrowing and no myocardial damage. Pain might have been due to transient coronary insufficiency associated with left ventricular failure.

*Case* 63. After partial recovery from left ventricular failure this man was pulled up on effort by a choking sensation in the throat accompanied by vague præcordial pain. Dyspnœa always preceded this sensation. Rest brought quick relief. The heart weighed 900 g. (the largest in the series). The coronary arteries were greatly enlarged and showed smooth outlines free from any points of narrowing. Histologically the myocardium was healthy except for a few microscopic points of fibrosis at the apex and base of the left ventricle. The fibrosis was focal and of the type frequently seen with myocardial ischæmia. The findings suggest that in spite of their enlargement the coronary arteries may have been inadequate to supply the enormous bulk of cardiac muscle, and pain may have been due to relative coronary insufficiency.

*Case* 65. This woman, during the last two months of her life, developed substernal pain on effort, radiating to the right side of the neck, to the axillæ, and passing down the inner sides of both arms to the elbows. It lasted ten minutes or so, and was associated with numbness and whiteness of the right hand for about twenty minutes. It was worse in cold weather, and was relieved by rest. The heart weighed 450 g. Skiagrams showed the coronary arteries to be of good size and free from narrowing. The myocardium showed no damage. Coronary spasm was probably responsible for the pain.

It is concluded that atypical thoracic pain in the course of hypertensive heart disease may be due to relative coronary insufficiency associated with left ventricular failure, to coronary spasm, to massive pulmonary embolism, or to pericarditis.

## Mode of Death

Thirteen of the fifteen ischæmic cases died from the disease itself—ten of them abruptly and, in a sense, unexpectedly, and the other three slowly in congestive heart failure.

In contrast, only eleven of the twenty-three hypertensive cases with cardiac symptoms died from heart disease. Only two died suddenly—one with a dissecting aneurysm of the aorta, the other while under the influence of too much digitalis. The other nine died slowly in congestive heart failure, and continuous cardiograms at the time of death in three of them showed that the mechanism was not ventricular fibrillation or sudden standstill, but a slowly increasing depression of conduction.

## Symptoms and Signs

*Cerebral symptoms.* Symptoms resulting from disturbances of the cerebral circulation, apart from Cheyne-Stokes breathing, which was associated with heart failure in both groups, were confined to the hypertensive cases, with the exception of one patient with ischæmic heart disease who had a stroke. The following conditions were noted: blurring of vision due to papillœdema (4 cases), sometimes progressing to blindness (2); severe headaches (6); mental deterioration (4); cerebral hæmorrhage (4); cerebral thrombosis (4); and hypertensive encephalopathy (1).

*Renal symptoms.* Nocturia occurred in five of the ischæmic and in twelve of the hypertensive cases. Uræmia developed in six of those with hypertension, but not in the others.

*Peripheral vascular symptoms.* Two of the hypertensive group exhibited the Raynaud phenomenon, and one intermittent claudication. Symptoms of peripheral vascular disease were not present in the patients with ischæmic heart disease.

*Body-weight.* In the ischæmic group bodyweights ranged from 6 stone 7 pounds to 13 stone 7 pounds, and on the whole were average. Of the women, two were unduly obese and two were unduly thin; of the men only one weighed more than 13 stone.

In the hypertensive group, six patients were very obese, their weights ranging between 14 and 22 stone. In twelve cases there was considerable loss of weight (1 to 7 stone).

*Cardiac rhythm.* The rhythm was normal in ten of the fifteen ischæmic cases: permanent auricular

fibrillation was present in one, paroxysmal auricular fibrillation in three, paroxysmal auricular flutter in two, and paroxysmal tachycardia in one. These seven rhythm changes occurred in five different patients. The fact is stressed that permanent auricular fibrillation occurred in only one case; indeed it only occurred once in the larger clinical series of fifty-six cases.

In the hypertensive group the rhythm was normal in twenty-one instances; auricular fibrillation occurred in the remaining six and was permanent in five of them. Other rhythm changes were not observed. Permanent auricular fibrillation occurred in 10 per cent of the larger series.

Of the six patients with auricular fibrillation, four had heart failure; or, putting it in another way, four out of eleven patients with heart failure had auricular fibrillation. Again, out of sixteen hypertensive patients without heart failure, only two had auricular fibrillation.

Contrasting the two groups it is seen that auricular fibrillation is more common in hypertensive than in ischæmic heart disease.

*Cardiac impulse.* The character of the cardiac impulse was described as forceful or thrusting in only three of the fifteen patients with ischæmic heart disease. Usually it was impalpable. In the hypertensive group, on the other hand, it was described as heaving in nineteen. This difference is considered significant and important.

*Valves.* Apart from one patient with organic mitral incompetence, due to concomitant rheumatic heart disease, there were no valve lesions in the ischæmic group. Aortic incompetence, however, occurred in four of those with hypertensive heart disease. It might be better described as an aortic leak, and appeared to be due to dilatation of the aortic ring resulting from high blood pressure. There was no peripheral vascular evidence of reflux and the diastolic blood pressure was not lowered. Seven patients had a mitral systolic murmur, and two had a soft mitral diastolic murmur. Both types of murmur were attributed to dilatation of the left ventricle.

*Fundi.* Apart from one patient with a combination of hypertensive and ischæmic heart disease and one with a single small exudate, the fundi were normal in the ischæmic group. In those with hypertension, on the other hand, marked hypertensive retinopathy with papillœdema, exudates, and hæmorrhages occurred in seven instances, exudates and hæmorrhages without papillœdema in one, and either exudates or hæmorrhages alone in two others. It may be concluded that significant changes in the fundi are part of the hypertensive picture and do not occur in association with ischæmic heart disease in the absence of diabetes (there were no such cases in this series).

*Peripheral arteries.* In eight out of the fifteen ischæmic cases the peripheral arteries were hardened. Eleven of the twenty-seven patients with hypertension had similar vessels; in the remainder the arteries were unduly firm and rubbery, but could not be described as hard.

*X-ray appearances.* The hearts of ischæmic cases were enlarged only when there was evidence of past or present failure, hypertension, or some other form of heart disease. Since only one patient had permanent auricular fibrillation it is not possible to comment upon the effect of this rhythm on the size of the ischæmic heart; for in that one case there was concomitant rheumatic heart disease with organic mitral incompetence. No instance of cardiac aneurysm was observed, but absence of pulsation in the region of the infarct was sometimes noted. Following heart failure (all those with failure had myocardial infarction), an enlarged cardiac shadow was always seen, the left ventricle being mainly involved.

In the hypertensive group the largest heart shadows were those associated with congestive failure. Cases without symptoms, or with effort dyspnœa only, showed slight to moderate enlargement of the left ventricle.

It is concluded that uncomplicated ischæmic heart disease does not cause cardiac enlargement, that uncomplicated hypertension causes hypertrophy of the left ventricle, and that heart failure is responsible for maximum cardiac enlargement in both groups.

*Electrocardiograms.* In the ischæmic group cardiographic changes were those of myocardial infarction when present. The features indicated anterior infarction in the first instance in seven, and posterior in four. Two showed signs of both anterior and posterior infarction, and two had normal curves.

In the hypertensive group sixteen out of twenty-four showed left axis deviation with depression of the RS–T segment in lead I, and of these eight also showed inversion of the T wave in lead I, and three inversion of the T wave in leads I and II. Two patients had left bundle-branch-block. Two had left axis deviation without other changes. In the remaining four there was no axis deviation but there was inversion of the T wave in lead I (Case 49), in leads I and II (Case 8), in leads II and III (case 69), and in leads I, II, and III (Case 19). All those with heart failure showed significant changes.

It is concluded that left axis deviation with depression of the RS–T segment with or without inversion of the T wave in lead I, or in leads I and II, is the

typical cardiographic pattern of severe hypertensive heart disease: this pattern was not observed in a single case of myocardial ischæmia. In cases of old-standing anterior myocardial infarction with persistent inversion of the T wave in lead I, there was no depression of the RS–T segment.

The hypertensive pattern with T I inverted was found in a third of the hypertensive group and in two out of twenty-eight mixed cases in the larger clinical series.

*Blood pressure.* The average blood pressure of six ischæmic cases prior to myocardial infarction was 180/95: after infarction the average pressure in eleven cases was 125/80. In the majority many readings were obtained: the highest average figure following infarction was 160/110. In two patients the blood pressure was taken immediately after an attack of myocardial infarction and was found to be elevated: in both these cases it dropped slowly following the initial rise and did not reach its lowest level until the third or fourth day. This delayed fall of blood pressure following myocardial infarction, with or without an initial rise, has been observed repeatedly in other cases in the clinical series. Attention is drawn to this fact and also to the frequency of moderate elevations of blood pressure found in ischæmic heart disease prior to myocardial infarction, elevations that are rarely accompanied by enlargement of the heart. Of fifty-six cases in the clinical series the blood pressure was less than 165/95 in 74 per cent.

The blood pressures of the hypertensive cases were necessarily high owing to the arbitrary classification employed. The average range was 245/140–190/115. The highest individual figure was 300/170, and the lowest 110/80. There were several features of interest.

First, there was no case in which the blood pressure was observed to drop as a result of heart failure. A terminal fall was common, but heart failure had often preceded this by weeks, months, or years.

Secondly, when the blood pressure fell much, there was usually an obvious cause. This was hæmorrhage in one case, shock from a strangulated hernia in another, massive pulmonary embolism in a third, and impending death in two others.

Thirdly the onset or cessation of auricular fibrillation, which was observed in Case 38, did not effect the blood pressure, whether there was heart failure or not (when there was fibrillation the pressure recorded was that at which most of the beats came through, and not the maximum pressure which was always higher).

Fourthly, two patients usually had normal pressures when at rest in bed, whether in heart failure or otherwise; but when up and about the figures climbed to over 200/110 with or without heart failure. One of these patients lived for seven years following the onset of cardiac symptoms—a record for the series.

*Renal function.* No case of pure ischæmic heart disease was complicated by serious impairment of renal function as judged by urine concentration and by the urea clearance test. In the whole ischæmic group there was only one case with bad renal function, and that was a case with associated hypertensive heart disease. Even albuminuria was very rare apart from heart failure.

The hypertensive cases, on the other hand, frequently showed considerable impairment of renal function, and six of them died with uræmia. Twelve out of twenty-seven had less than 44 per cent of normal renal function as judged by the urea clearance test. Albuminuria occurred in all but one; granular casts were found in seven; there was considerable impairment of urine concentration in ten.

It may be concluded that impairment of renal function is a feature of the hypertensive state, and is unrelated to ischæmic heart disease.

*Blood count.* There was not a single case with anæmia in the ischæmic group, but there were two with polycythæmia. In contrast to this, nine hypertensive patients were anæmic, the red cell count being under 4,000,000 per c.mm., or the hæmoglobin being under 60 per cent.

## Difference between Ischæmic and Hypertensive Heart Disease

The chief differences between ischæmic and hypertensive heart disease are shown in Table II. The evidence is based on the clinical features alone, and will be reviewed later in the light of the autopsy findings which were not known when the table was compiled.

## Pathological Findings

To obtain the desired pathological information, a technique had to be devised that would enable us to form an accurate estimate of the capacity of the coronary lumina during life, to trace the exact position of any vascular or myocardial lesions, and to preserve the tissues for histological study. It was decided that these requirements would be met by injecting the coronary arteries with a radio-opaque gel, followed by radiography and subsequent clearing of the whole heart after the method of Gross (1921). In order that the degree of vascular distension should be comparable with that obtained during life, all cases were injected at the known diastolic pressure of the patient. The only

TABLE II

THE CHIEF DIFFERENCES BETWEEN ISCHÆMIC AND HYPERTENSIVE HEART DISEASE

| Feature | Ischæmic cases (15) | Hypertensive cases (27) |
|---|---|---|
| Complaint | Pain. | Breathlessness. |
| Sex | Male : female = 2 : 1. | Male : female = 1 : 1. |
| Age | Males av. 56·5 years.<br>Females av. 67·8 years. | Males av. 59·2 years.<br>Females av. 54·6 years. |
| Onset | Dyspnœa in 20%.<br>Usually pain. | Dyspnœa in 75%.<br>Sometimes fatigue or dropsy. |
| Course | Temporary good recovery in 40%.<br>Myocardial infarction in 13 out of 15. | Temporary good recovery in less than 10%.<br>Development of infarction necessitating change of classification—1 case. |
| Mode of death | Cardiac death 13/15 (abrupt 10/13). | Cardiac death in 11/23 (abrupt 2/11). |
| Symptoms from disturbances of the cerebral circulation. | Rare apart from cerebral thrombosis. | Blurring of vision: 4<br>Blindness: 2<br>Severe headaches: 6<br>Mental changes: 4<br>Cerebral hæmorrhage: 4<br>Cerebral thrombosis: 4 |
| Renal failure | Very rare.<br>Renal function tests usually good.<br>Albuminuria rare apart from heart failure. | Six died with uræmia.<br>Van Slyke less than 44% in 12 out of 27.<br>Albuminuria in all but one. |
| Fundi | Normal in all but one. | Hypertensive retinopathy in 10 out of 27. |
| Blood count | Anæmia did not occur.<br>Polycythæmia in 2. | Anæmia in 9/27. |
| Rhythm | Permanent auricular fibrillation 1. | Permanent auricular fibrillation 5. |
| Cardiac impulse | Forceful or heaving in 3; usually impalpable. | Heaving in 19; usually located with ease. |
| Valves | Normal. | Aortic leak in 4. |
| Blood pressure | Average 180/95 before infarction.<br>Average 125/80 after infarction. | Av. range: 245/140 to 190/115. |
| X-ray | Normal prior to heart failure.<br>Always enlarged after development of heart failure. | Slight to moderate enlargement prior to heart failure.<br>Considerably enlarged after development of heart failure. |
| Electrocardiogram | Normal or typical changes of myocardial infarction.<br>The pattern described in the hypertensive column was not seen in a single case. | Left axis deviation with depression of the RS–T segment with or without inversion of the T wave, usually in lead I alone, sometimes in leads I and II, in 75%. |

exception to this was in the case of normal controls in which the blood pressure was not known. In these cases a standard pressure of 90 mm. Hg. was used.

The apparatus (Fig. 1) consisted of a simple fluid column leading down from an adjustable container and connected to a mercury manometer. This was filled with warmed normal saline and served to wash out the blood from the coronary vessels and also to supply the required head of pressure for injection. The fluid column lead directly to a Y piece connected to two cannulæ for perfusing the heart, but was connected also to a shunt circuit containing two bottles, one to act as a pressure chamber and the other to contain the injection mass. When this circuit was shut off, the apparatus perfused saline through the coronary vessels; but when the direct circuit was closed and the shunt circuit opened, the saline displaced the air from the pressure chamber into the bottle containing the injection mass, driving the latter into the cannulæ. The barium-gelatine injection mass was prepared according to the technique of Gross.

*Procedure.* At autopsy the heart was carefully dissected out, clots were dislodged and the heart weighed. It was then placed in normal saline and left at room temperature until it was injected a few hours later (usually three hours). The proximal parts of both coronary arteries were then defined and under-run with ligatures. Two cannulæ were then tied in, the whole manœuvre being carried out under water at 37° C. This warmed the heart to body temperature and also prevented any bubbles entering the coronary arteries. The heart was then perfused with normal saline at 37° C until the fluid issuing from the coronary sinus was relatively clear (about 1 minute). The circuit was then changed, and the warm gelatine mass injected at the same pressure. When the mass could be seen to have entered the fine arterioles in the pericardium, the

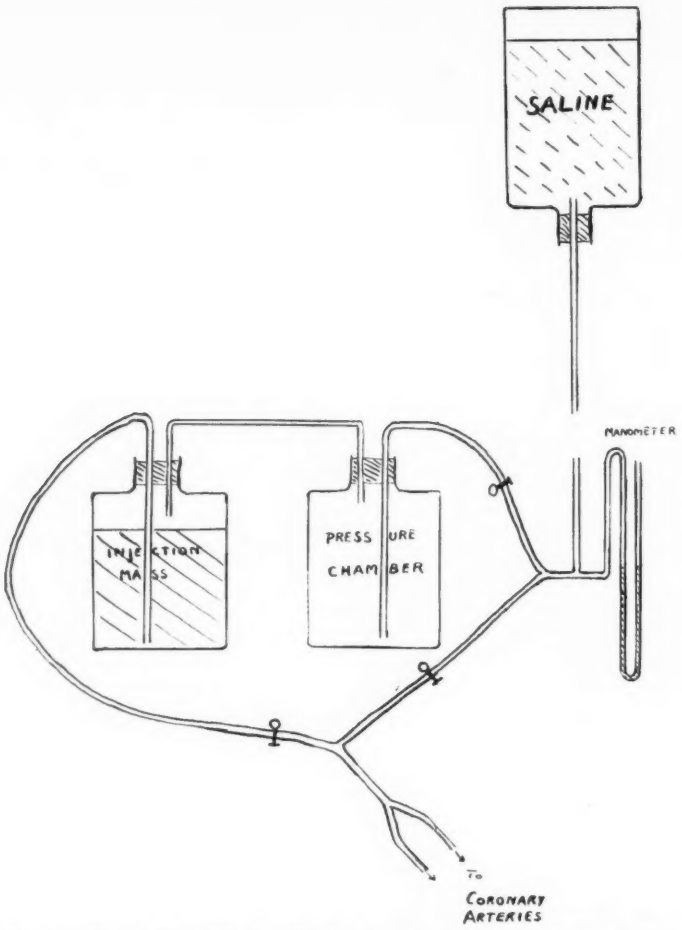



FIG. 1.—Apparatus used for injecting the coronary circulation with barium gel. For description see text.

heart was placed in iced water until the gelatine had set, and then transferred to a bath of formol-saline for 24 hours. Stereoscopic skiagrams were then taken according to standard technique. The heart was then returned to formol-saline and left to fix for about ten days. Next, four routine blocks of myocardium were excised and frozen sections stained for fat. These were taken from the apices of the left and right ventricles anteriorly and from the bases of the ventricles posteriorly. Special blocks were also taken from other sites as indicated. The heart was then passed through increasing concentrations of alcohol from 30 per cent to absolute alcohol, in steps of 10 per cent, remaining about three days in each bath. By this means complete dehydration was obtained in about three weeks.

Old used alcohol was utilized for the lower concentrations, fresh absolute alcohol being employed only for the final one or two baths. This proved satisfactory and saved considerable quantities of alcohol. When the heart was dehydrated it was transferred to a bath of used methyl salicylate and later to fresh methyl salicylate. By this means the tissue was rendered relatively transparent. The coronary vessels, which stood out clearly owing to

the presence of the opaque injection mass, could thus be studied in detail and compared with their skiagrams.

Blocks for section were then taken from the major coronary vessels (8 or more) and from the myocardium (5 or more). The myocardial blocks were obtained from five standard sites: the anterior apical and posterior basal parts of the right and left ventricle, and the upper anterior part of the interventricular septum. Additional blocks were taken from any other sites that showed anatomical changes. The blocks were washed in chloroform over night and embedded in paraffin.

## Results

*Normal controls.* Twelve normal controls, representing each decade of life from the third to the eighth, were examined by the standard technique (Fig. 3 and 7). In no case was there any evidence of heart disease or of high blood pressure either during life or at autopsy. The details of the cases are given in Table III. It is not proposed to discuss in detail the normal findings in injected hearts. This has already been done by Gross (1921) and in so far as the normal anatomy of the coronary tree is concerned, our findings are in agreement with his.

But we would add the important observation that coronary atheroma is compatible with an apparently normal lumen. In all twelve of this series the skiagrams showed normal coronary outlines (Fig. 3), yet coronary atheroma was subsequently discovered in five, and was severe in three. In this connection it should be noted that the size of the coronary lumen in a paraffin section gives little or no indication of its real size during life. It was repeatedly noted both in normal and pathological hearts that where sections showed coronary narrowing, skiagrams might reveal no abnormality.

It is of course open to question how far such skiagrams reflect the state of the vessels during life; but we believe that, with the technique employed, they give the truest picture that can be obtained from an autopsy specimen. In contrast to the pathological cases, normal controls with atheroma showed no trace of myocardial fibrosis.

A second finding not emphasized by Gross was the relationship between the size of the coronary arteries and the size of the heart. Since all skiagrams were taken by a standard technique the plates are comparable as regards size. In all cases the three major coronary arteries (left anterior descending, left recurrent, and right) were measured near their origins. From their diameters their total cross-sectional area was calculated and plotted against the weight of the heart. The resulting graph (Fig. 2) showed a fairly close scatter around a straight line, and indicates that there is a direct relationship between the bulk of the cardiac muscle and its blood supply.

TABLE III

Control Cases: Size of Heart and of Coronary Artery

| Case No. | Age | Sex | Heart weight (grams) | Total coronary bore (sq. mm.) | Coronary atheroma (microscopic) | Cause of death |
|---|---|---|---|---|---|---|
| 12 | 22 | F | 225 | 27·9 | — | Subarachnoid hæmorrhage |
| 35 | 23 | F | 213 | 38·1 | — | Polyposis coli |
| 21 | 24 | F | 165 | 18·9 | — | Carcinoma of colon |
| 76 | 34 | F | 280 | 29·7 | — | Carcinoma of stomach |
| 72 | 39 | M | 282 | 36·5 | ± | Acute appendicitis |
| 77 | 47 | F | 190 | 32·3 | — | Carcinoma of cervix uteri |
| 1 | 54 | M | 265 | 20·0 | + | Seminoma of testis |
| 14 | 55 | M | 200 | 28·7 | + | Carcinoma of œsophagus |
| 10 | 56 | F | 308 | 32·0 | — | Bronchitis |
| 64 | 61 | M | 365 | 59·0 | — | Carcinoma of lip |
| 26 | 73 | F | 310 | 39·4 | + | Primary carcinoma of liver |
| 27 | 80 | M | 400 | 36·5 | ± | Cirrhosis of liver |
| | | | *Hypertrophied controls* | | | |
| 67 | 46 | M | 495 | 46·6 | — | Cor pulmonale |
| 71 | 60 | M | 495 | 41·8 | — | Syphilitic aortic incompetence |
| 54 | 71 | F | 585 | 51·5 | ± | Osteitis deformans. Heart block |
| 20 | 60 | M | 643 | 44·4 | — | Rheumatic mitral and aortic disease |
| 59 | 64 | M | 850 | 71·6 | ± | Rheumatic aortic incompetence |

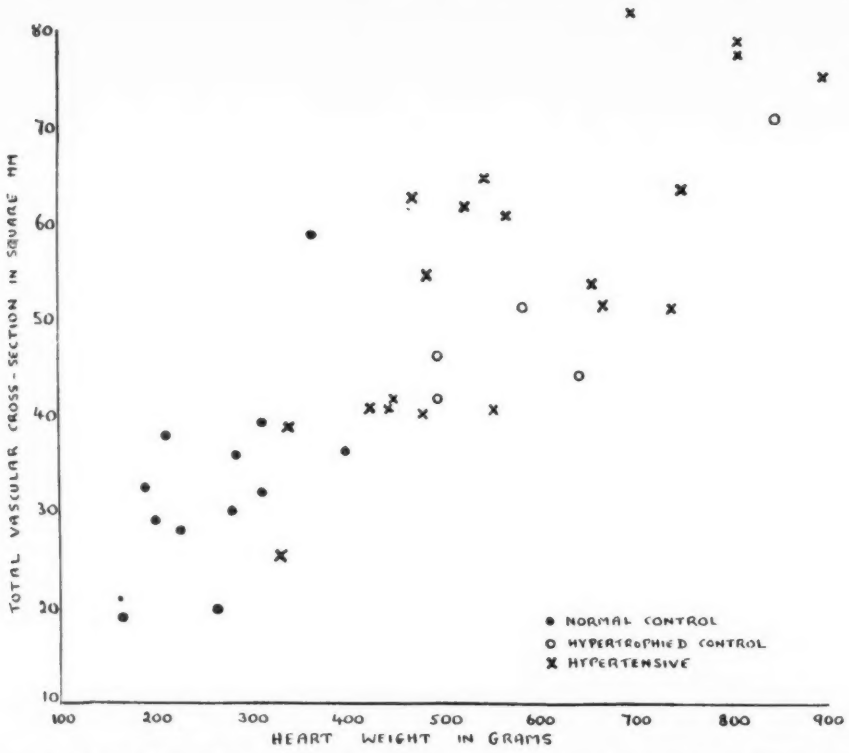



FIG. 2.—Graph illustrating the linear relationship between the heart weight and the total cross-section of the main coronary vessels in normal controls, controls with hypertrophied hearts, and in cases of hypertensive heart disease.

### HYPERTENSIVE GROUP

It soon became apparent that the pathological findings were totally different in the two types of case. Though the differences in morbid anatomy and histology between ischæmic and hypertensive heart disease are well known, the dissimilarity was emphasized by the skiagrams. The ischæmic hearts showed narrow coronary vessels with irregular outlines, and, as a rule, one or more complete occlusions (Fig. 6, 9, and 10). The hypertensive hearts, on the other hand, showed large wide coronary arteries with smooth outlines and no narrowing. There were a certain number that showed evidence of both hypertension and ischæmia.

This group comprised twenty-seven cases of clinical hypertensive heart disease, subdivided into four groups according to their severity (page 205). The main pathological findings are summarized in Table IV.

*Heart weight.* All but two showed cardiac hypertrophy, the mean cardiac weight for the whole group being 597 g. ±149 g. It will be noted from Table IV that the degree of cardiac hypertrophy expressed as total heart weight is fairly closely related to the clinical severity of the disease judged by the functional state of the heart. In the cases that ran a full cardiac course and died in congestive failure, the mean weight was 729 g. In the cases that showed evidence of left heart failure but did not die a cardiac death, the mean heart weight was 585 g. In those with effort dyspnœa only the mean weight was 492 g. Finally, in the four cases with no cardiac symptoms, the mean weight was only 406 g.

In all cases the increased cardiac weight was mainly due to left ventricular hypertrophy. Right ventricular hypertrophy was difficult to estimate. Owing to the hearts being cleared intact it was no

TABLE IV

HYPERTENSIVE CASES: SIZE OF HEART AND CORONARY ARTERIES

*Died without cardiac symptoms*

| No. | Age | Sex | Blood pressure | Heart weight (grams) | Total coronary bore (sq. mm.) | Coronary atheroma | | Myocardial fibrosis | | R.V. hypertrophy | Mode of death |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | X-ray | Micro. | Retic. | Focal | | |
| 24 | 63 | F | 260/120 | 340 | 39·0 | — | + | — | — | + | Pulmonary embolism |
| 47 | 63 | F | 250/130 | 485 | 55·2 | — | — | ± | — | — | Cerebral hæmorrhage |
| 60 | 46 | F | 280/140 | 470 | 63·0 | — | ± | + | — | — | Uræmia |
| 69 | 21 | F | 250/130 | 330 | 25·3 | — | — | — | — | — | Uræmia |
| | | | | | *Died with effort dyspnœa* | | | | | | |
| 23 | 44 | F | 225/130 | 425 | 41·1 | — | — | + | — | ± | Cerebral hæmorrhage |
| 36 | 58 | F | 220/135 | 545 | 64·8 | — | ± | + | — | ± | Herniotomy |
| 39 | 68 | M | 210/100 | 525 | 62·0 | — | ± | — | — | — | Herniotomy |
| 43 | 87 | F | 230/150 | 440 | — | ± | + | — | + | + | Pneumonia |
| 44 | 49 | M | 290/140 | 570 | 60·8 | — | + | — | — | ± | Cerebral hæmorrhage |
| 65 | 44 | F | 230/120 | 450 | 42·3 | — | ± | + | — | — | Hæmatemesis |
| | | | | | *Died with left ventricular failure* | | | | | | |
| 11 | 56 | M | 243/125 | 700 | 82·4 | — | + | + | — | + | Cerebral hæmorrhage |
| 13 | 67 | F | 260/125 | 447 | 41·1 | — | ± | + | — | — | Uræmia |
| 19 | 42 | F | 260/160 | 480 | 40·6 | — | ± | — | — | — | Uræmia |
| 41 | 64 | F | 280/145 | 575 | — | + | + | — | — | ± | Uræmia |
| 45 | 54 | F | 260/120 | 660 | 53·8 | — | ± | — | — | + | Uræmia |
| 68 | 67 | M | 200/125 | 650 | — | ± | + | + | — | — | Pneumonia |
| | | | | | *Died in congestive cardiac failure* | | | | | | |
| 8 | 60 | M | 250/150 | 695 | — | ± | + | + | + | + | |
| 28 | 69 | M | 150/120 | 750 | 63·8 | — | ± | + | — | + | |
| 32 | 50 | M | 170/115 | 670 | 51·7 | — | — | + | ± | + | |
| 38 | 53 | M | 270/140 | 738 | 51·5 | — | + | — | — | + | |
| 48 | 51 | M | 220/125 | 710 | — | ± | + | + | ± | + | |
| 49 | 54 | F | 200/100 | 810 | 79·3 | — | ± | + | ± | + | |
| 50 | 54 | M | 190/140 | 820 | — | + | + | + | + | + | |
| 53 | 59 | F | 190/110 | 555 | 41·1 | — | ± | + | — | + | |
| 58 | 66 | M | 210/140 | 810 | 78·1 | — | ± | + | — | + | |
| 62 | 68 | M | 220/135 | 560 | — | + | + | — | + | — | |
| 63 | 60 | M | 180/110 | 900 | 76·1 | — | ± | + | ± | + | |

possible to dissect off the right ventricle and weigh it separately; moreover, after clearing, it was considered that estimates of hypertrophy were of doubtful value owing to shrinkage. An attempt was made to estimate the degree of right ventricular hypertrophy histologically and the results are given in Table IV. Hypertrophy was obvious in fourteen cases, slight in four, and absent or unrecognizable in nine. The incidence of right ventricular hypertrophy in the different groups is of interest. In the eleven cases that died in congestive heart failure, right ventricular hypertrophy was present in all but one: this one was complicated by severe coronary sclerosis. It is assumed that this hypertrophy was due to the strain thrown on the right heart by failure of the left ventricle.

The same explanation may be given for cases of right ventricular hypertrophy in the second group; for although these patients did not die in congestive failure, they had evidence of left ventricular failure during life. In the other two groups there was insufficient left ventricular failure to account for

right ventricular hypertrophy. Case 43, however, was complicated by emphysema, and Case 24 by old pulmonary embolism. The remainder showed very slight, if any, hypertrophy. Apart from hypertrophy the myocardium appeared healthy in twenty-six cases. In the twenty-seventh (Case 62) there was macroscopic evidence of infarction.

*Endocardium.* One (Case 48) showed calcification of the aortic valve of Mönckeberg type, not causing appreciable stenosis or incompetence. All other cases were free from valve disease.

### *Radiography*

It will be most convenient to describe first the typical findings in this group and then to discuss the

FIG. 3.—Normal control. Case 76. Heart 280 g. skiagram of injected heart. Note size of coronary arteries and their smooth outlines. (All skiagrams are 0·6 of natural size and are comparable.)

exceptions. The most striking feature was enlargement of the coronary arteries (Fig. 4 and 5). In 20 this enlargement was conspicuous; the outlines of the coronary lumina were perfectly smooth and there was no suggestion of irregularity or focal narrowing. The degree of coronary enlargement appeared to increase pari passu with hypertrophy of the heart. When the three main coronary arteries were measured in the same way as the controls and their total cross sectional area plotted against the cardiac weight (Fig. 2), a fairly close scatter around a straight line was observed, which proved to be a continuation of that previously described in controls. This strongly suggests that the size of the coronary arteries is dependent on the size of the heart, and that they enlarge in response to

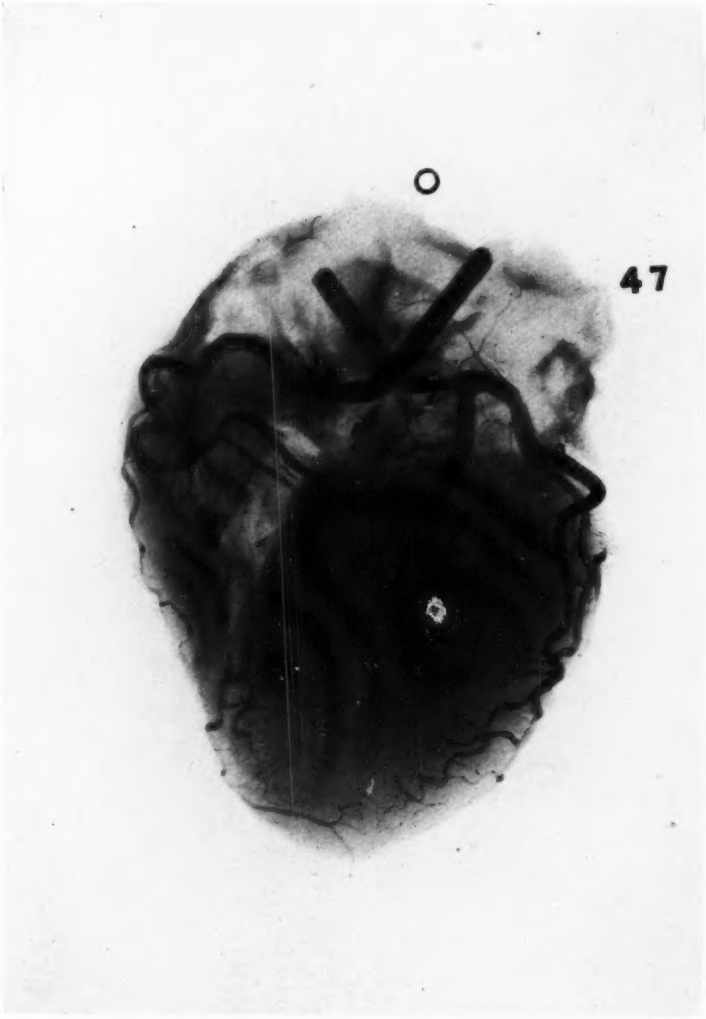



FIG. 4.—Hypertensive heart disease. Case 47, died before cardiac symptoms arose. Heart 485 g. Note enlargement of heart and coronary arteries and the smooth outlines of the latter.

an increased demand. There is, however, an alternative explanation, namely that the coronary arteries are dilated by the raised pressure within them, or that the pressure at which they were injected caused them to dilate more than controls injected at lower pressure. The latter possibility is refuted by the fact that two hypertensive cases (Cases 49 and 53) injected at low pressure (because the diastolic pressure had fallen some time before death) revealed coronary arteries as large as any injected at higher pressures.

To investigate the possibility that coronary dilatation was the direct result of raised blood pressure during life, we injected five cases of cardiac hypertrophy due to other causes, namely, rheumatic valvular disease (Cases 20 and 59), syphilitic aortic

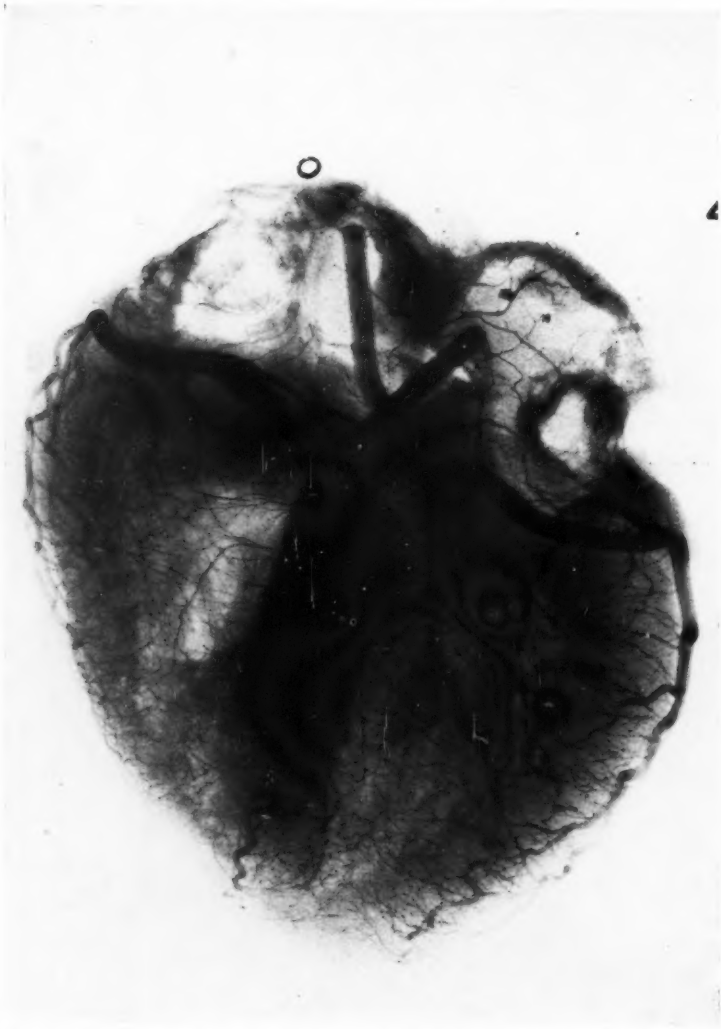


FIG. 5.—Hypertensive heart disease. Case 49, died of congestive failure. Heart 810 g. Note enormous heart and coronary arteries and the smooth outlines of the latter.

regurgitation (Case 71), cor pulmonale (Case 67) and osteitis deformans (Case 54), all showed a degree of coronary enlargement similar to that seen in hypertensive heart disease (Fig. 2). It is concluded that coronary vascular enlargement is related to cardiac hypertrophy.

Seven out of the twenty-seven cases showed some evidence of occlusive coronary atheroma in the skiagrams. In four (Cases 8, 48, 43, 68) this was slight, constituting no more than minor irregularities of outline and relatively small calibre in relation to the size of the heart; there were no points of gross narrowing. In three of these cases the myocardium showed a few small foci of fibrosis: in the fourth no lesion was detected. Each of the other three (Cases 41, 50, 62) showed severe coronary sclerosis

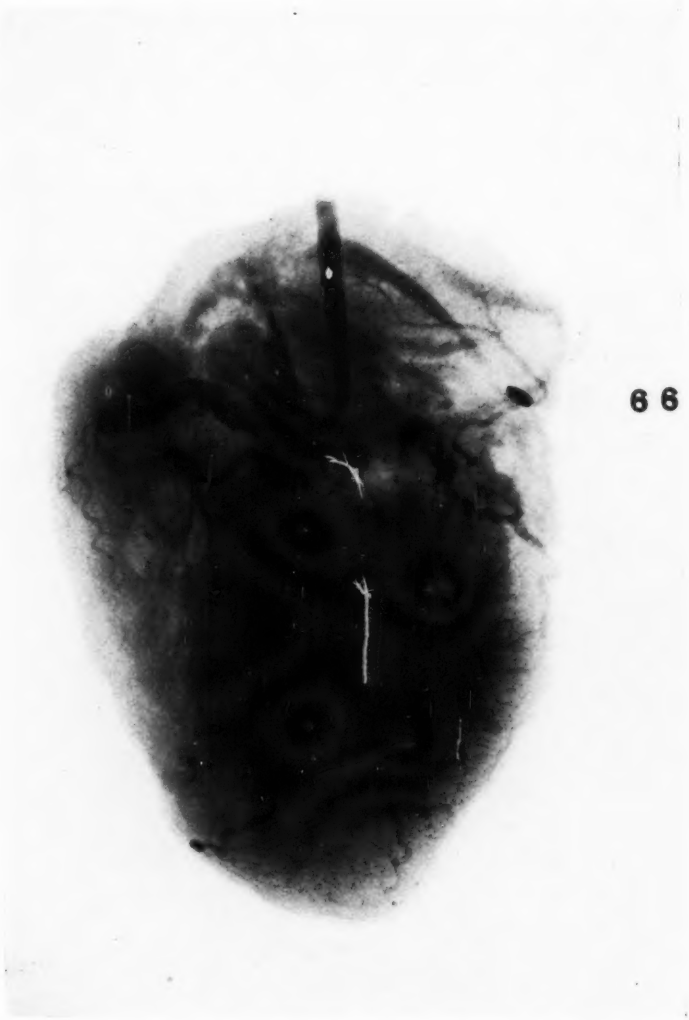



FIG. 6.—Ischæmic heart disease. Case 66. Heart 565 g. Note narrow irregular, calcified coronaries with several occlusions.

with narrowing of the lumen, at least one complete occlusion, and evidence of myocardial ischæmia. Clinically it is interesting to note that Cases 50 and 62 died suddenly. Case 41 died in uræmia.

*Cleared specimens.* All cases were subjected to "clearing" in methyl salicylate, the cleared specimens (Fig. 8) being compared with the skiagrams. This confirmed the conclusions drawn from the latter and was of great value in selecting segments of the coronary vessels for histology. It did not, however, add any further information. Cleared specimens were not used for measurements owing to the shrinkage that occurs in the process of clearing.

*Histology. Coronary arteries.* Twenty-three cases (all but Cases 23, 32, 47, and 69) showed histological evidence of atheroma; yet the skia-

FIG. 7.—Normal control. Case 35. Heart weight 213 g. Cleared specimen showing white injection mass filling lumen of coronary arteries. Note the perfectly smooth outlines.

grams of sixteen of them exhibited normal coronary outlines, confirming the observation made in the controls that atheroma need not narrow the lumen. Atheroma in these cases was relatively slight and of patchy distribution. The seven cases that showed narrowing or irregularity of the arteries in the skiagrams all showed severe and generalized atheroma histologically. Two other features deserve comment. In adult life normal coronary arteries have a well developed intima thicker than that of other arteries of similar size (von Glahn, 1936). In the hypertensive cases this layer tended to be thicker than in controls. Secondly, the media was hypertrophied.

An unexpected finding was polyarteritis nodosa in Case 32. This affected the majority of the small

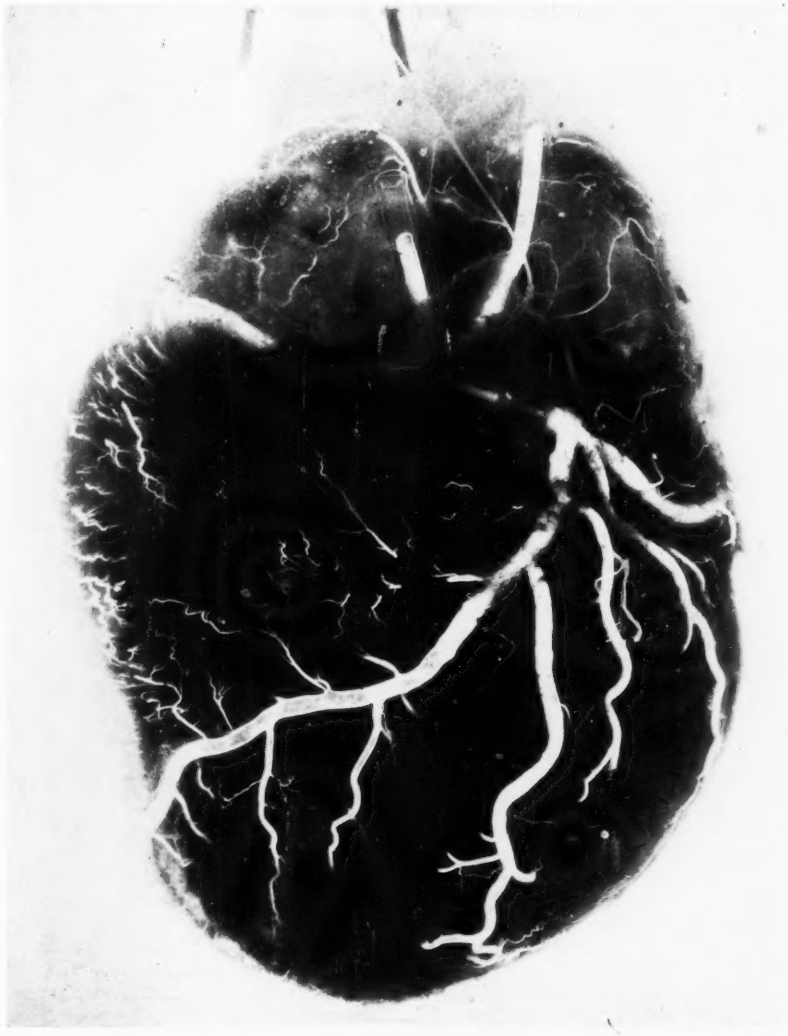


FIG. 8.—Hypertensive heart. Case 36. Heart weight 545 g. Cleared injected specimen showing dilatation of coronary lumen and smooth outlines, indicating absence of occlusive coronary atheroma.

arteries throughout the body, but most of the coronary vessels were spared.

*Histology. Myocardium.* Evidence of hypertrophy has already been described. In addition, however, necrosis was seen in two cases. In Case 62 there were recent infarcts at both the apex and base of the left ventricle following severe coronary atheroma and thrombosis. In Case 41 there were numerous adjacent foci of infarction at the apex of the left ventricle, following thrombosis of the descending branch of the left coronary artery.

*Fatty change.* Fatty degeneration of slight or moderate severity was found in fourteen out of the twenty-seven cases. It did not appear to be correlated with the size of the heart, with the state of the coronary circulation, or with any other known factor, and we have therefore been unable to attach any significance to it.

*Myocardial fibrosis* was seen in the hypertensive cases in three forms, which we have called healed infarcts, focal fibrosis, and reticular fibrosis. The only example of a healed infarct was in Case 62 in which it was associated with an old coronary occlusion.

Focal fibrosis took the form of small foci (under 1 mm.) in which the muscle fibres had been replaced by collagen. In most cases replacement was complete, but occasionally necrotic muscle fibres were still visible. This lesion, which was seen with greater frequency and severity in the ischæmic group, occurred in seven of the hypertensive group (Cases 8, 32, 43, 48, 49, 50, and 63). The skiagrams of four of these (Cases 8, 43, 48, and 50) showed coronary narrowing, but in the other three (Cases 32, 49, and 63) the coronary arteries had uniformly wide lumina and smooth outlines. Case 32 had polyarteritis and since some of the smaller vessels in the myocardium were involved (but not the main coronary vessels) it is fair to assume that fibrosis was the result of occlusion of small vessels. Cases 49 and 63 died in congestive failure, and fibrosis might be attributed to relative coronary insufficiency; but we must point out that the vessels were large and free from any obstruction.

The third type of fibrosis, which we have called reticular, was always associated with gross muscular hypertrophy. It occurred in seventeen cases and took the form of an exaggeration of the normal interstitial reticular connective tissue fibres. In the normal heart these are extremely fine and can only be satisfactorily demonstrated by silver impregnation, but in cases of gross hypertrophy they thickened and became clearly visible as fine collagenous fibres surrounding the muscle fibres (Fig. 11). This form of reticular fibrosis tended to occur in foci and for this reason might be mistaken for ischæmic focal fibrosis. We believe, however, that it is a separate entity for the following reasons. Firstly, it was not seen in any of our pure ischæmic hearts; secondly, it is limited to cases of gross myocardial hypertrophy; thirdly, we were never able to demonstrate any sign of muscle loss. We consider that it is a form of concomitant fibrous tissue hypertrophy.

*Renal changes.* The hypertensive cases were classified according to their cardiac condition, and though most were examples of essential hypertension, a few proved to be secondary to chronic nephritis. In practice the histological differentiation between nephritis and advanced arteriosclerotic kidney is extremely difficult, particularly since Ellis (1942) has shown that primary nephritis may persist with hypertension as the dominant clinical sign and arterial damage as the dominant renal change. In spite of these difficulties we have attempted to classify the kidneys in this series into hypertensive and nephritic. Seven (Cases 11, 19, 41, 47, 65, and 69) showed evidence of nephritis whilst the remaining twenty showed varying degrees of arterial damage, from a few hyaline vessels up to severe changes of the type classified as malignant hypertension. Six of the hypertensive group died in uræmia and four of these (Cases 19, 41, 45, and 69) were among those with histological evidence of nephritis. The other two (Cases 13 and 60) showed the histological appearances of malignant hypertension.

### Ischæmic Cases

There were fifteen cases in this group, and their main pathological findings are summarized in Table V.

*Heart weight.* The hearts were all hypertrophied except in Case 25. The mean weight for the whole group was 495 g. $\pm$76 g., the range being 350–650 g. Such a degree of hypertrophy suggests that either ischæmic hearts may become hypertrophied during their course or that our cases were complicated by hypertension. It will be seen from Table V that eight cases had some degree of hypertension during life. The mean heart weight of these was 497 g., whilst the mean heart weight of those without hypertension was 494 g. Thus there is no correlation between heart weight and hypertension in this series. On the other hand, if the cases are divided according to the duration of cardiac failure, some correlation becomes apparent. Those with left ventricular failure for two months or more (6 cases) had a mean heart weight of 549 g. $\pm$56 g.; whereas those with terminal or no congestion (9 cases) had a mean heart weight of 459 g. $\pm$60 g. The difference

TABLE V
ISCHÆMIC CASES

| Case No. | Age | Sex | Blood pressure | Heart weight (grams) | Coronary* occlusion site | Myocardial† | | Mode of death |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Fibrosis | Necrosis | |
| 17 | 57 | F | 158/92 | 432 | L.D. | | L.V.A. | Syncope |
| 22 | 76 | F | 170/85 | 480 | L.D. | L.V.A. | I.V.S. | Congestive cardiac failure |
| 25 | 71 | F | 140/60 | 350 | L.D., R. | L.V.A., L.V.P. | L.V.A., L.V.P. | Syncope |
| 29 | 43 | M | 172/120 | 480 | L.D., L.C. | L.V.A. | L.V.A., O.M. | Syncope |
| 30 | 53 | M | 150/110 | 535 | L.D., L.C. | L.V.A., O.M. | | Syncope |
| 37 | 60 | M | 184/80 | 590 | R. | L.V.A. | L.V.P. | Congestive cardiac failure |
| 40 | 47 | M | 120/80 | 580 | L.D., L.C. | L.V.A., L.V.P. | L.V.P. | Lung abscess |
| 42 | 61 | M | 220/140 | 425 | | | L.V.A. | Syncope |
| 46 | 55 | M | 190/100 | 400 | L.D., R. | L.V.A. | L.V.P. | Hæmopericardium |
| 51 | 65 | M | 95/60 | 495 | R. | | L.V.P., R.V.P. | Sepsis |
| 52 | 53 | M | 120/80 | 480 | L.D., L.C. | L.V.A. | L.V.A., L.V.P. | Congestive cardiac failure |
| 55 | 71 | F | 175/105 | 630 | L.D., R. | | L.V.P. | Congestive cardiac failure |
| 66 | 69 | M | 140/80 | 656 | L.C., R. | O.M. | L.V.P., R.V.P. | Myocardial infarction |
| 70 | 63 | M | 140/105 | 480 | L.C., R. | L.V.P. | L.V.P. | Myocardial infarction |
| 73 | 64 | F | 180/110 | 505 | L.D., L.C., R. | L.V.P., L.V.A. | L.V.A., L.V.P. | Congestive cardiac failure |

* L.D.=Left descending branch. L.C.=Left circumflex branch. R.=Right coronary.
† L.V.A.=Left ventricle anterior. L.V.P.=Left ventricle posterior. R.V.P.=Right ventricle posterior. O.M. =Obtuse margin. I.V.S=Interventricular septum.

is 90 g. and the standard error of the difference is 9·7 g. This correlation between duration of failure and heart weight is similar to our finding in the hypertensive group, and is further evidence that cardiac failure is an important factor in the production of myocardial hypertrophy.

*Coronary arteries.* The skiagrams (Fig. 6) and cleared specimens (Fig. 9 and 10) of the injected coronary vessels in the ischæmic cases showed a characteristic picture, quite different from that of the hypertensive group. The characteristic feature was the constant presence of severe narrowing or occlusion, usually both. There was, of course, some variation in the degree and extent of the lesions. In eight cases the whole coronary tree was affected and all the major arteries were narrowed and irregular in outline, often with deposits of calcium salts in their walls. Complete occlusions in both right and left coronary arteries were usually demonstrable.

In the other seven cases arterial narrowing was limited either to one vessel (usually the left) or to part of a vessel, whilst the rest of the coronary tree was relatively normal. In some of these cases the unaffected vessels were wider than normal. The mean heart weight was slightly higher (527 g.) in cases with localized coronary narrowing than in those with generalized coronary narrowing (460 g.). Out of four with no history of angina of effort (Cases 17, 30, 40, and 51), three were examples of localized coronary narrowing.

Coronary occlusion was commonly multiple as previously indicated, though in one case it was incomplete, and in four it was single; there were eight cases with two blocks and two cases with three blocks. The distribution was as follows: out of twenty-six complete occlusions eighteen were in the left coronary artery and eight in the right. Myocardial infarction was found in thirteen out of fourteen cases with one or more complete occlusions. The case without complete occlusion had no infarct but only microscopic foci of necrosis. The other (Case 37) without infarction had a solitary occlusion of the right coronary artery, and showed only microscopic necrosis. Amongst the other thirteen cases there were fourteen healed infarcts and eleven recent infarcts, all but one involving the left ventricle. The areas affected were the apex anteriorly (11 cases), the base posteriorly (10 cases), the obtuse margin (3 cases) and the base of the right ventricle posteriorly (1 case). In each of these twenty-five infarcts the appropriate coronary artery was completely occluded. There was no correlation between the type of lesion present and the mode of death. Syncopal deaths were not particularly associated with recent thrombi or infarcts.

Anastomotic vessels, just big enough to be visible in the skiagrams, were noted in all cases. These occurred in relation to the distal parts of occluded vessels, and sufficed to permit retrograde filling of these vessels. They were better seen in the "cleared" specimens (Fig. 9 and 10).

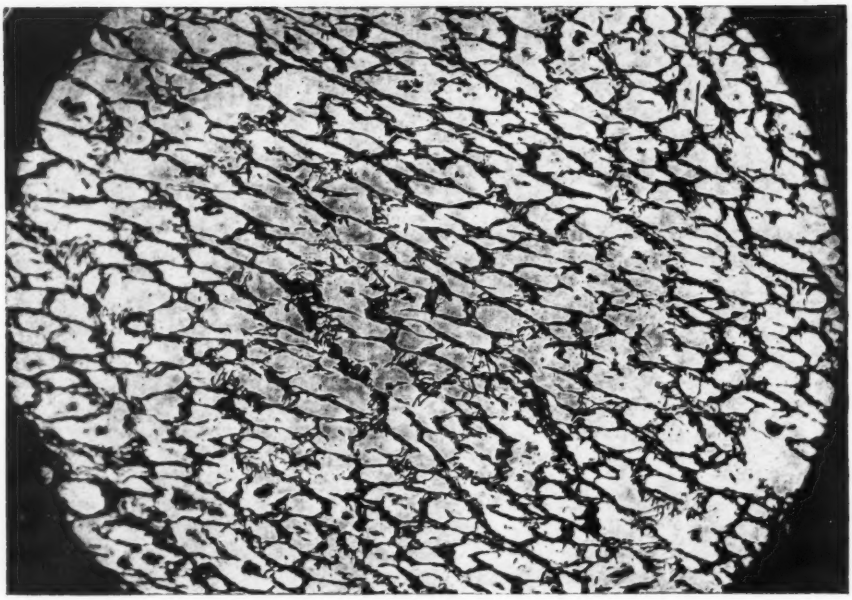
*Histology. Coronary vessels.* With certain reservations histological study of the coronary

arteries confirmed the radiographic findings. In most of the skiagrams, however, no matter how irregular or narrowed the majority of the vascular lumina, some segments still looked normal both in calibre and in smoothness of outline; yet microscopically these parts also showed severe atheroma. A similar discrepancy was observed both in the controls and in the hypertensive cases, but it is repeated for emphasis that even in manifest ischæmic heart disease, the appearance of atheroma in a section of a coronary artery does not necessarily indicate narrowing *in vivo* at that site. Again, it was quite impossible to tell from the skiagrams whether a focus of narrowing was due to atheroma or to a recanalized thrombus. On numerous occasions points of narrowing noted in the ski-

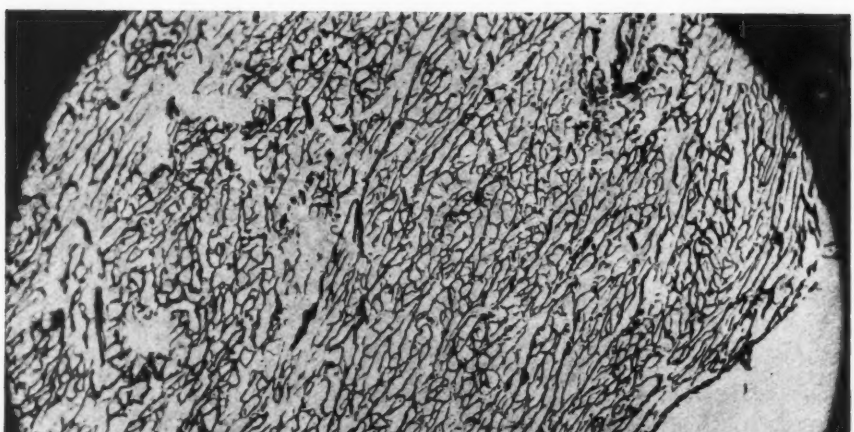
FIG. 9.—Ischæmic heart. Case 46. Anterior view showing small coronary arteries with irregular outlines, complete occlusion in right coronary artery, and anastomoses via pericardial vessels.

grams and in cleared specimens proved to be healed thromboses in which the recanalized lumen was as large as the adjacent narrowed atheromatous vessel. This may explain the occurrence of myocardial infarction in the presence of patent, though narrowed, vessels; for the absence of complete occlusion at autopsy does not prove the vessel was never blocked during life. These examples of organized recanalized thrombi were ones in which the histological diagnosis was unequivocal, but apart from these there were many others in which such an interpretation would be difficult to refute. In late cases of recanalized thrombosis, the fibrous tissue replacing the thrombus fuses with atheromatous lesions so intimately that we were often unable to tell whether a given lesion was atheromatous or thrombotic. This difficulty was accentuated when atheromatous lesions showed undue vascularity of hæmorrhage as described by Winternitz *et al.* (1938). Both phenomena were observed in some sections or the coronary arteries in nearly every case. When the vasa vasorum were small the hæmorrhages were fresh, it seemed fair to assume that they were late effects of atheroma; but when the vasa were large and ran parallel with the coronary artery, and when blood in the plaque was represented only by groups

FIG. 10.—Ischæmic heart. Case 25. Showing recanalized occlusion of the descending left coronary artery and irregularity of outline in others.



A



B

FIG. 11.—Section of heart muscle. (A) *Hypertensive heart disease* (*Case* 11), and (B) *Control* (both magnified × 108) showing hypertrophy of interstitial connective tissue in myocardial hypertrophy " reticular fibrosis." Silver impregnation.

of macrophages filled with pigment, it became impossible to decide whether or not there had been thrombosis. This similarity lends support to the hypothesis recently put forward by Duguid (1946) that what is ordinarily regarded as coronary atheroma is, in fact, the result of organized thrombi.

*Myocardium.* The histological appearances of the myocardium in the present series of cases conformed to the accepted descriptions of ischæmic heart disease, but there were two points that merit some discussion. The first is the time relation between coronary closure and myocardial infarction. In the majority of cases these corresponded. Recent infarcts were associated with recent thrombi and old infarcts with old thrombi. Furthermore, they were associated in position, the infarcts occurring in sites supplied by occluded vessels. We did not observe any cases in which infarction was due to the closure of a vessel supplying the infarcted area only by anastomoses, though this has been observed by Blumgart *et al.* (1940). We did, however, observe three examples (Cases 29, 46, and 55) in which recent infarction was unassociated with recent thrombosis in any vessel big enough to be visible macroscopically. In two of these (Cases 29 and 46) the symptoms of the fatal infarct arose at home whilst the patient was at rest, and the lesion cannot therefore be attributed to unusual circulatory demands beyond the capacity of the coronary supply. It is possible that a period of diminished cardiac output may have reduced the coronary flow sufficiently to have precipitated the infarcts, but there was no evidence available on this point. Coronary spasm can almost certainly be excluded on the grounds that the coronary tree was too rigid for this to be possible. These cases are of importance because they may represent the late counterpart of cases of sudden death in ischæmic heart disease where neither recent occlusion nor fresh infarction is demonstrable at autopsy. It is possible that such cases, which are common in forensic practice, might show infarction if they survived long enough.

The second feature noted in the present series was the development of minute foci of necrosis leading to focal fibrosis. These small lesions, usually just visible macroscopically, were encountered in ten of the sixteen cases, often in several sites in one heart. We were able to observe every stage of their development, and they showed exactly the same changes as do ordinary infarcts, but on a minute scale. It appears to us desirable that these lesions should be regarded as minute infarcts, and that the term ischæmic fibrosis should imply this. In most cases these small lesions were found to be related, both in time and site, to occluded coronary branches, but this was not always so. Minute infarcts without demonstrable vascular occlusion presumably have the same pathogenesis as their larger counterparts.

## Discussion

*Previous history.* The high incidence of a history of rheumatic fever in both hypertensive and ischæmic groups is regarded as coincidental, for necropsy revealed evidence of rheumatic heart disease in but one case, and the known facts deny relationship. Thus, of 542 cases with granular kidney reported by Pitt (1887), 6 per cent had mitral stenosis. Of 403 clinical hypertensives analysed by Boas and Fineberg (1926), 8 per cent had mitral stenosis. Of 1000 hypertensive cases studied by Bechgaard (1946), 1 per cent had clinical evidence of mitral stenosis. Finally, in 122 hypertensive subjects under 50 years of age, Haloven and Salomaa (1947) found a history of rheumatic fever in 6·6 per cent, compared with an incidence of 9·8 per cent in 250 controls. Although figures from the paper by Pit and by Boas and Fineberg, and also those given by Levine and Fulton (1928) show that about 40 per cent of cases of mitral stenosis have hypertension, it must be remembered that 33 per cent of men aged 40, and 43 per cent of women aged 40, have a blood pressure of 150/100 or above (Master *et al.*, 1943). Claims that the rheumatic process may involve the coronary vessels (Plesch, 1947) cannot be denied; but there is no statistical evidence implicating rheumatic fever as an important ætiological or contributory agent in the development of the common form of ischæmic heart disease.

*Family history.* Platt's suggestion that essential hypertension may be a hereditary disease transmitted as a Mendelian dominant with a rate of expression of over 90 per cent (Platt, 1947) cannot be easily dismissed. Thus it may be calculated trom Berchgaard's findings in over 1000 hypertensive subjects that the incidence of high blood pressure in the parents was about 75 per cent (Bechgaard, 1946), and the author considered that about 20 per cent of his cases were renal in origin—a group in which the hereditary factor has been shown to play no part.

The hereditary aspect of ischæmic heart disease has been less frequently studied, and has been rarely separated from the hypertensive group. General opinion, however, strongly favours hereditary predisposition.

*Age and sex.* Our figures bear out the well-known difference in sex and age incidence. The ratio of males to females is usually given as about 4 : 1 in ischæmic heart disease, whereas it is close to 1 : 1 in essential hypertension. It is also recognized that the preponderance of males in ischæmic

heart disease is proportional to the age of the groups studied. Thus it is overwhelming in those under 40; 8 to 1 in those between 40 and 49; 4 to 1 in those between 50 and 59; 2 to 1 in those between 60 and 69; and the sex ratio is equal in those over 70 (Hedley, 1939; Gordon *et al.*, 1939).

*Clinical features.* The steady downhill course of hypertensive heart disease was well illustrated, and contrasted sharply with good temporary recovery in at least one-third of the ischæmic cases. This latter behaviour may be attributable to coronary thrombosis with or without infarction, followed by improvement in the collateral coronary circulation.

More than half the hypertensive group died from non-cardiac causes, chiefly uræmia or cerebral hæmorrhage. Only two died suddenly. On the other hand, ten out of fifteen ischæmic cases died abruptly. This confirms the well-known fact that ischæmic hearts are peculiarly liable to develop ventricular fibrillation, but it also demonstrates that hypertensive hearts are not.

Of great interest was the rarity with which cases initially classified as hypertensive later developed angina pectoris or myocardial infarction. The pathological studies provide a ready explanation for this, for they show that the typical hypertensive heart has smooth distended coronary arteries. It is not denied that about 66 per cent of ischæmic cases have a blood pressure over 150/90, (Master *et al.*, 1936), or that nearly 50 per cent have a blood pressure at least 160/100 (Riseman and Brown, 1937); but we agree with the latter authors that systolic pressures over 200 are rare. It must be repeatedly pointed out that about half of the population between the ages of 50 and 60 have blood pressures of 150/100 or above (Master *et al.*, 1943), and it is therefore misleading to quote similar figures in ischæmic heart disease, which involves particularly this age-group, as evidence that coronary disease is intimately related to hypertension. The difference in the quality of the cardiac impulse in the two groups and in the size of the heart as viewed fluorscopically, was most impressive.

The pathological findings proved conclusively that the hypertensive electrocardiographic pattern showing left axis deviation with depression of the RS–T segment with or without inversion of the T wave in lead I was not due to coincident coronary disease nor to myocardial fibrosis, but appeared to closely related to the size of the left ventricle. Likewise, auricular fibrillation and bundle-branch-block occurring in hypertensive heart disease could not be ascribed to ischæmic fibrosis. Admittedly, bundle-branch-block was twice as common in ischæmic as in hypertensive heart disease in the clinical series, occurring in 10 per cent and 20 per cent of the cases respectively.

## Pathological Features

The most striking observation in the injected hearts was the basic difference in the coronary pattern between the hypertensive and ischæmic series and the lack of overlap between them. It is probably true that hypertension does predispose to coronary sclerosis, but our findings suggest that the relationship has been overstressed. Confusion may have arisen on account of the frequency at autopsy of enlarged hearts with atheromatous coronary arteries—it being assumed that the hypertrophy indicates previous hypertension and atheromatous coronary arteries indicate ischæmia. Either of these assumptions may be false. Our observations show that in coronary sclerosis cardiac failure can produce myocardial hypertrophy to an average weight of 550 g. irrespective of a raised blood pressure. This has been observed by Bartels and Smith (1932) and by Davis and Blumgart (1937), and Eyster (1927, 1928) has suggested that stretching of the heart by dilatation is the essential stimulus to hypertrophy. In spite of this, the assumption is still commonly made that a heart weight of over 500 g. indicates hypertension. Another source of error is the assumption that atherosclerosis must cause coronary narrowing. Stewart *et al.* (1935) showed that this was not so and our present findings confirm this. It is not suggested that atheroma does not lead to ischæmia but we believe that by ordinary examination it is very difficult to estimate whether or not the vessels are narrowed during life.

Our observation that the coronary arteries enlarge as the heart hypertrophies confirms the previous findings of Gross (1921), Russow (1936), Fishberg (1937) and Sagebial (1934), but in addition they strongly suggest that the degree of coronary enlargement keeps pace with the needs of the heart and that " relative " ischæmia is not a cause of cardiac failure in hypertension. The concept of relative ischæmia has probably arisen from the finding of myocardial fibrosis unassociated with appreciable coronary sclerosis Such fibrosis may be of the type which we have called reticular and which we believe to be a form of fibrous tissue hypertrophy and not an indication of muscle destruction. This was also the view of Stadler (1907). Alternatively, there are undoubtedly cases of focal myocardial fibrosis indistinguishable from healed infarcts but unassociated with any coronary occlusion. Such cases have been observed by Blumgart (1940, 1941), Gross and Sternberg (1939), Ravin and Greeves (1946) and by Holyoke (1945), as well as by us. We suggest that it is more reasonable to attribute them to a diminu-

tion of coronary flow during a phase of cardiac failure than to postulate either relatively small coronary arteries or spasm.

## Summary and Conclusions

Comparative clinical and pathological studies have been made on twenty-seven cases of hypertensive heart disease and fifteen cases of ischæmic heart disease. There were twelve controls.

Hypertensive cases were characterized clinically by even sex distribution, dyspnœa, steady deterioration, retinopathy, cerebral symptoms, impairment of renal function, anæmia, auricular fibrillation, and by clinical, radiological, and cardiographic evidence of left ventricular enlargement before the onset of heart failure. Only one case originally classified as hypertensive developed subsequent angina pectoris or myocardial infarction. Death was rarely abrupt.

Ischæmic cases were characterized clinically by an unequal sex distribution favouring men, the older age of women, the infrequency of early dyspnœa, the absence of anæmia, of retinopathy and of cerebral symptoms, good renal function, normal rhythm, normal heart size before failure, good temporary recovery, and by abrupt death.

At autopsy the hearts were investigated by injection of the coronary arteries followed by stereoscopic radiography and dissection and histological examination. The following conclusions were drawn.

Moderate degrees of coronary atheroma do not necessarily cause narrowing.

The size of the coronary arteries varies directly with the heart weight in both normal and hypertrophied hearts irrespective of the cause of the hypertrophy.

The coronary arteries vary sharply between hypertensive and ischæmic cases: in the former they are large with smooth bores, in the latter they are narrow and frequently occluded.

In hypertensive cases the heart weight varies with the degree of failure during life and not with the height of the blood pressure.

The coronary size increases as the heart size increases and there is no evidence to indicate relative ischæmia of the ventricular muscle.

In severely hypertrophied hearts the normal fibrous tissue increases in thickness.

In ischæmic cases cardiac hypertrophy is the rule and can be correlated with the duration of failure.

Myocardial infarction can occur in the apparent absence of coronary occlusion, and is probably then due to circulatory failure.

We are deeply indebted to Dr. Duncan White for his kindness in taking stereoscopic skiagrams in all cases. We also wish to thank Mr. J. Baker and Mr. J. Griffin for the many hundreds of slides they prepared and Mr. V. Willmott for the photographs.

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# SINO-AURICULAR BLOCK, INTERFERENCE DISSOCIATION, AND DIFFERENT RECOVERY RATES OF EXCITATION IN THE BUNDLE BRANCHES

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Disturbances in the propagation of the heart beat between the auricle and the two ventricles are of frequent occurrence and well known under the terms A-V dissociation or heart block. The term sino-auricular block is the standard name for an apparent block between the sinus node and the auricle, a hypothetical incident to explain transient auricular standstill for a period of time that is a multiple of the length of the regular sinus cycle. Interference dissociation is commonly associated with a nodal rhythm with retrograde block, the slower sinus excitation and auricular beat being conducted intermittently to the ventricle. Less commonly, interference dissociation is seen in cases of near complete A-V dissociation, with occasional sinus beats being conducted in a favourable time period, a phenomenon usually attributed to the likelihood that junctional tissues have a supernormal phase of excitation and conductivity following their refractory period. Some of the best examples of this phenomenon are the first case of Lewis and Master (1924), the cases of Wolferth (1928), of Luten and Pope (1930), of Pareja (1933), and the first case of Burchell (1942).

Electrocardiographic records obtained recently from a woman, aged 60, exhibited the recurring phenomenon of nodal rhythm with interference dissociation in which the ventricular beat conducted from the auricle showed the presence of either left or right bundle branch block. The unique feature was the fact that the type of bundle branch block exhibited was determined by the time relationship between the P wave that was to be followed by a ventricular response and the preceding R wave of the idioventricular (nodal) beat. The explanation seemed related to either different rates of recovery in conduction in the two bundle branches or a supernormal phase either of conduction in the left bundle or of excitation in the left ventricle. As there were, in addition, frequent cardiographic sequences showing the picture of sino-auricular block, the possible relationship of this abnormality to the disturbance in A-V and intraventricular conduction invited some speculation.

## Report of Case

A woman, 60 years of age, registered at the clinic with the main complaints of varicose veins, painful feet related to corns, mild shortness of breath, slight substernal discomfort with moderate exertion, and backache. No history was elicited that digitalis or other medicines had been taken. Auscultation of the heart revealed no murmurs. The blood pressure was 140 systolic and 90 diastolic. There were extensive varicosities of the veins of both legs and a stasis ulcer on the lower part of the left leg. The roentgenogram of the thorax showed moderate generalized cardiac enlargement. The roentgenogram of the spinal column showed a dorsal kyphosis and moderate osteo-arthritic changes. The cardiac diagnosis was coronary sclerosis and angina pectoris.

*Electrocardiographic study.* On the short cardiographic sequences obtained for routine evaluation there was noted an intermittent type of A-V dissociation during which occasional A-V conduction occurred. Only a few such complexes were present and the initial cardiographic diagnosis was probable A-V dissociation with interference dissociation, the occasional conduction being related to a supernormal phase of conduction. The patient returned the following day for more extensive study. For about the first fifteen minutes of electrocardiographic sampling, normal sinus rhythm was present and this was not affected by pressure on either carotid sinus. Then spontaneously a cardiac irregularity appeared

and a continuous record was obtained for approximately three minutes, during which about twenty-five premature beats were noted. The developed records showed phenomena similar to those of the preceding day but the abnormal mechanisms could be more definitely interpreted.

The various disturbances in rhythm and conduction are illustrated in Fig. 1 and 2. In Fig. 1, there are shown in the four tracings from above downward respectively, first, normal sinus rhythm with slight sinus arrhythmia, the P–P intervals varying from 1·24 to 1·56 sec.; second, sequences of S–A block, the heart being more rapid and the regular P–P intervals showing only slight variation and averaging 0·96 sec.; and third and fourth, nodal rhythm with interference dissociation in the simultaneously taken right and left præcordial leads. The third tracing shows three premature ventricular beats, the first having the complex of right bundle branch block, the second that of left branch block, and the third a normal QRS complex. The fourth tracing shows two premature right bundle branch complexes and one left, the latter being interpolated between two normal QRS complexes.

In Fig. 2, the top sequence shows the usual or classic picture of interference dissociation in which the nodal rhythmicity rate is faster than the sinus rate, and a retrograde block is present. The R–R intervals of the nodal rhythm measure 1·68 sec. and the P–P intervals of sinus rhythm 1·76 sec.; thus, the record shows that the P waves gradually appear later and later after the R wave until finally the junctional tissues are found non-refractory and an interference beat occurs, and in the record portrayed there is an associated prolonged P–R interval and left bundle branch block. In the lower tracing of Fig. 2 are shown three premature beats, the first with a left bundle branch block complex, the second with a normal QRS complex, and the third with a right bundle branch block, and then return of normal sinus rhythm. It is to be noted that the premature ventricular beats have a definite time relationship to a preceding P wave and, depending upon the interval between the P wave that is to be followed by conduction and the preceding R wave of the nodal beat, the ventricular complex will show left bundle branch block, right bundle branch block, or a normal QRS complex.

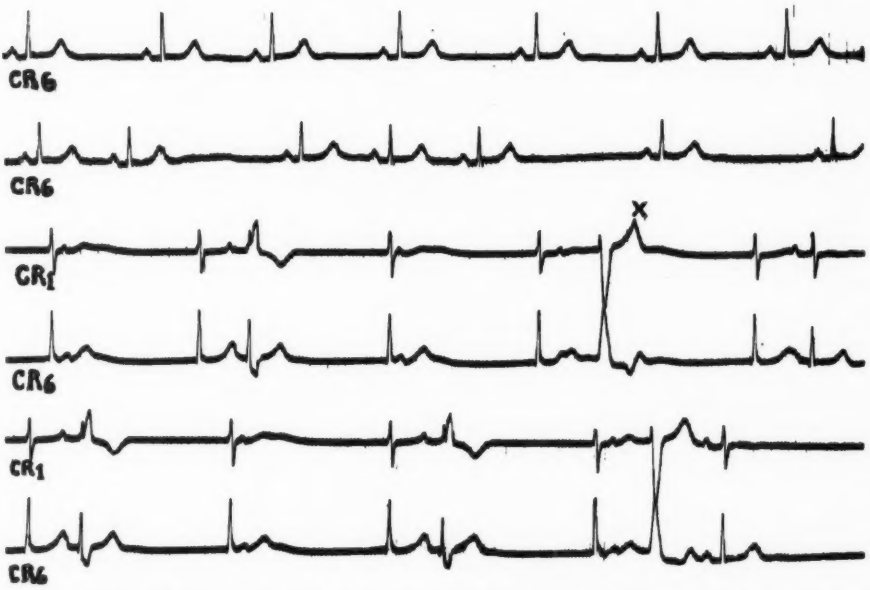


FIG. 1.—Electrocardiograms discussed in the text. Four sequences are shown. In the lower two pairs of records, simultaneous tracings from two præcordial positions are shown, position 1 being in the fourth interspace just to the right of the sternum, and position 6 being in the fifth interspace in the left midaxillary line. The indifferent electrode was on the right arm.

Particular attention needs to be paid to the left bundle branch block complexes in the third tracing in Fig. 1 and in the bottom tracing of Fig. 2 where the T wave is deformed (marked X) by an apparent P wave of abnormal shape. These P waves occurred commonly after the left bundle branch block complexes but never with the right bundle branch block complexes. While these P waves possibly are indicative of auricular extrasystoles, the constant association with the left bundle branch complexes and the preceding prolonged P–R interval suggest that such P waves represent a re-entry into the auricle, in fact indicating auricular reciprocal beating.

## Comment

The acceptance of the concept of a sino-auricular block is dependent only on the evidence of sudden excitation could not be readily measured. The frequent close association of a P wave with the R wave when a supposed nodal rhythm was present might theoretically be related to sino-ventricular conduction and partial sino-auricular block. The progressive increase in the R–P times in the sequence shown in Fig. 2 could be related to a progressive increase in S–A conduction time. The conducted beat of the interference dissociation sequence, if such premises were accepted, could then represent reciprocal rhythm. While a progressive increase in S–A time or a Wenckebach phenomenon has been claimed, on good evidence (Decherd *et al.*, 1945), to occur, it is most unlikely that the phenomenon of sino-ventricular conduction without auricular response would have occurred without many examples of dropped auricular beats having been observed. Orthodox views, however, regarding the

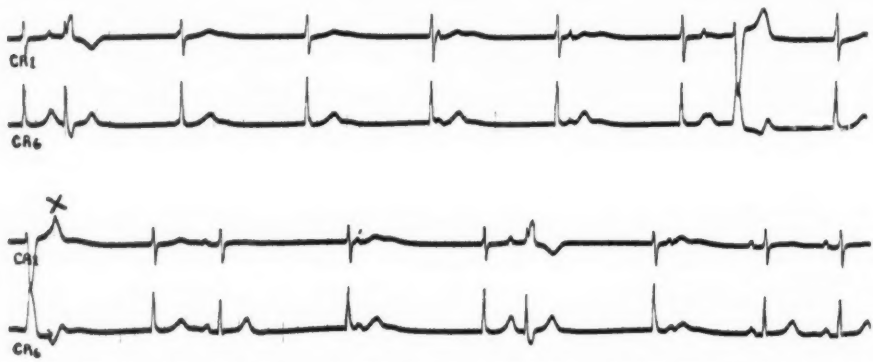


Fig. 2.—Electrocardiograms discussed in the text. Two pairs of records with simultaneously recorded præcordial potentials are shown.

halving of the auricular rate, and all the objections of Lewis (1925) to the term and its implications still pertain. In the case reported herein, the disturbance in sinus rhythm resulting in marked auricular slowing allowed a lower rhythm centre to drive the ventricle and permitted the development of circumstances that give the picture of interference dissociation. If there were specialized conducting pathways between the sinus node and the A-V node, as Eyster and Meek (1914 and 1922) interpreted their experiments to indicate, and if one were to assume the presence of an entrance block into the auricle, a curious phenomenon of a sino-ventricular beat without an auricular contraction could occur. As Lewis *et al.* (1914) incidentally noted in their criticism of Eyster and Meek's investigations, excitation potentials related to sino-auricula-ventricular nodal conduction without contingent auricular nature of nodal rhythm with and without retrograde conduction to the auricle would seem to be well agreed upon, and they are explained and illustrated in standard textbooks on electrocardiography. The relatively short intervals in ventriculo-auricular and auriculo-ventricular sequential beats during heart block has probably attracted the attention of many investigators, and the problem was reviewed by Wolferth and McMillan (1929), who emphasized that the auricular elements of the sequences were represented by abnormally shaped and usually inverted P waves. The possible auricular re-entry beats in this case (Fig. 1 and 2) associated with conduction defects in the main bundle and left bundle block complexes are particularly interesting in that there was never retrograde conduction to the auricle during the long sequences of nodal rhythm.

The only published electrocardiographic records seen that approach the nature of the tracings in the case reported herein are those shown in Fig. 196 of Scherf and Boyd's *Clinical Electrocardiography* (1946). The tracing is interpreted as showing extreme sinus bradycardia through 2 : 1 sinus block, with escaped beats and interference dissociation, with the conducted sinus beats showing an aberrant QRS complex owing to abnormal spread within the ventricle. The tracings demonstrating interference except for one conducted beat where there is impaired bundle branch conduction.

In the present case the number of observations seems sufficient to establish evidence of an absolute pattern of conduction in the main bundle and bundle branches dependent upon the time the P wave came after the R wave of the preceding nodal beat. The switch from left bundle branch block to right bundle branch block occurred at a critical time interval and was associated with a sharp decline in total A-V

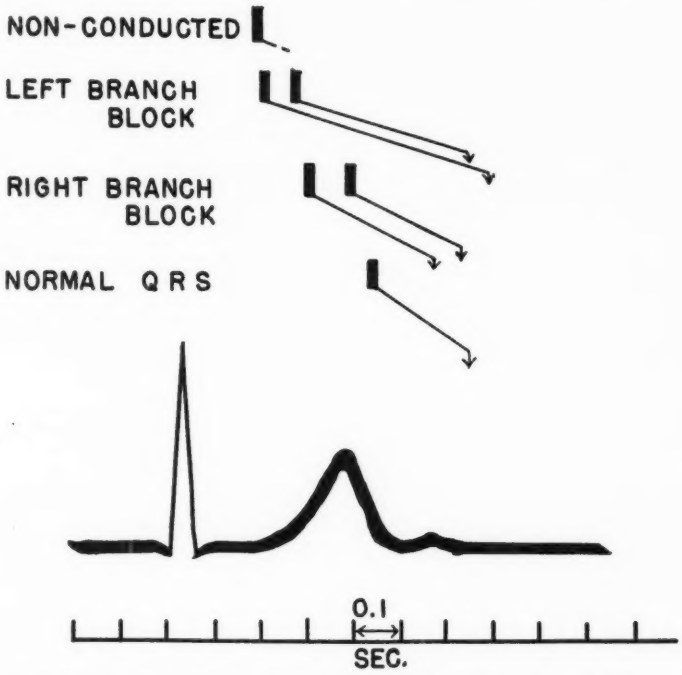


FIG. 3.—The diagrammatic illustration shows the relationship of P waves, represented by the black rectangles, to the preceding R wave of the nodal beat in respect to whether they are followed by left or right branch block complexes or a normal QRS complex. See text for explanation.

dissociation published by Jervell (1934) show complexes of the bundle branch form, but in these tracings nearly normal QRS complexes may occur with the same R–P and P–R intervals as those in which the intraventricular conduction defect is present.

The case in the paper by Cowan (1939) may have been similar to that of the case reported herein in that the records were said to show "variable sino-auricular block, the auricular rhythm being very irregular and infrequent." One tracing that was reproduced shows complete A-V dissociation

conduction (Fig. 3). With the sequences showing left branch block there was a definite tendency for the total A-V conduction time to be shorter as the P wave fell farther away from the preceding nodal complex, but with the right bundle block complexes the total A-V conduction time remained relatively constant (Fig. 4).

One of the main difficulties in appraising the nature of the conduction of the interference beat is the lack of knowledge of the exact origin of the nodal beat within the junctional tissues. If such know-

ledge were available the refractoriness of the upper and lower portions of the junctional tissues relative to one another might have been better estimated. The difficulties of interpreting the effects of blocked retrograde impulses on the refractoriness and possible supernormal phases of junctional tissues and myocardium have been emphasized by Langendorf (1948) and Mack *et al.* (1947).

One explanation of the phenomenon of the rapid alternation in the type of bundle branch block is illustrated in Fig. 5. It is assumed that the nodal beat originated in the upper portion of the junctional tissues so that the main bundle precedes that of the bundle branches in phases of excitation and refractoriness. The earliest P waves followed by conduction are shown to occur in the partially refractory state of the main bundle, and when the excitatory process reaches the bundle branches, the left bundle branch is completely refractory and the right partially refractory. Left branch block associated with partial right branch block is then present. The term " partial right branch block " is used as an equivalent to the term " partial heart block " when the latter means an abnormal prolongation of the P–R interval.

The diagram (Fig. 5) shows rapid recovery in the left branch so that an excitatory process traversing the main bundle at a later period travels more quickly through the left branch than through the right and a right branch block is manifest. A supernormal phase of conduction in the left branch might be added to the basis for the explanation but seems unnecessary. If the diagram as drawn were truly representative of the conditions, there would be a partial left branch block in addition to a manifest right branch block.

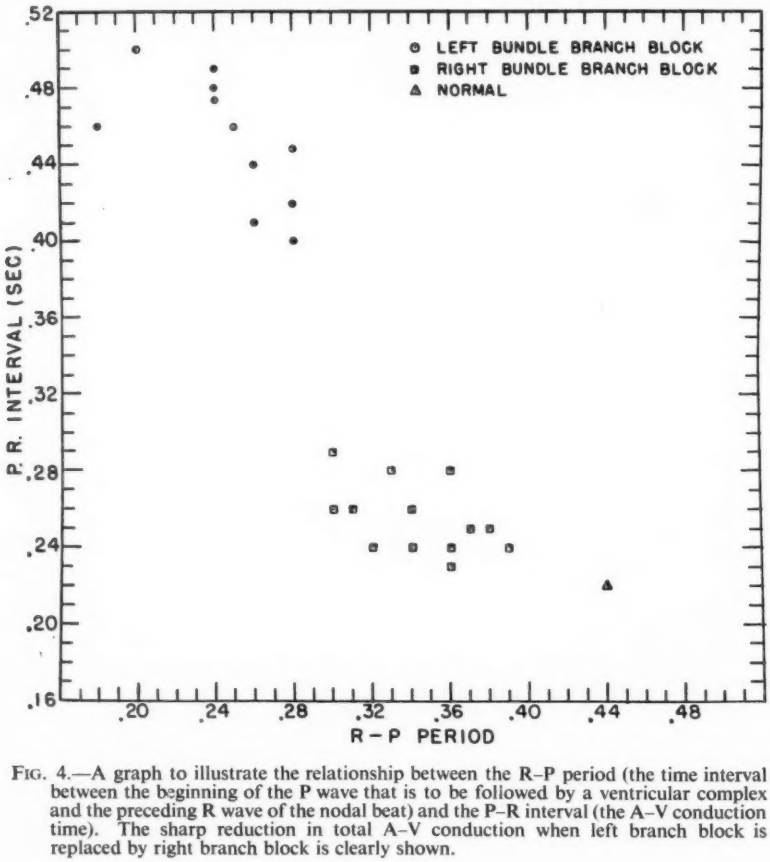


FIG. 4.—A graph to illustrate the relationship between the R–P period (the time interval between the beginning of the P wave that is to be followed by a ventricular complex and the preceding R wave of the nodal beat) and the P–R interval (the A–V conduction time). The sharp reduction in total A–V conduction when left branch block is replaced by right branch block is clearly shown.

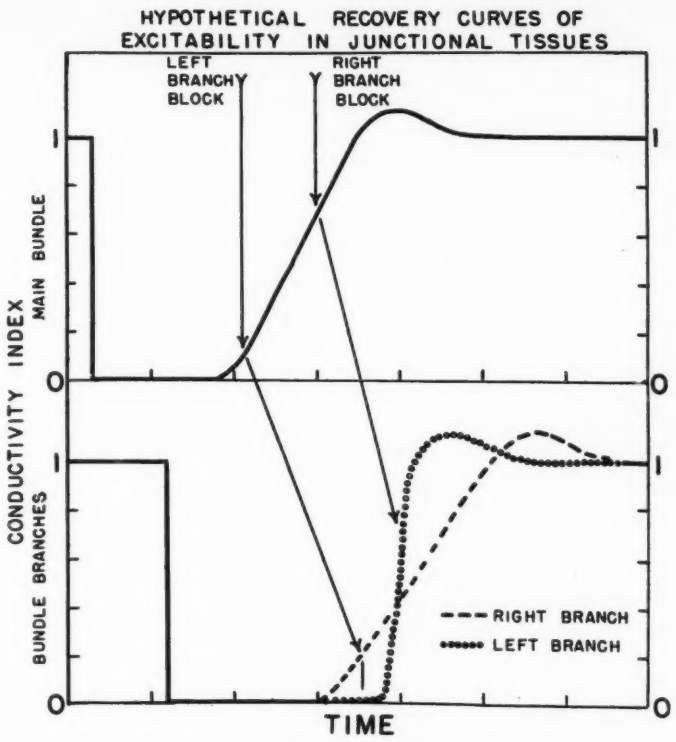


FIG. 5.—The diagram illustrates hypothetical " recovery of excitation curves," or periods of total and partial refractoriness, of junctional tissues. The conductivity index represents variations in refractoriness, O being total refractoriness and 1 being normal conductivity. The interpretation as applied to the case reported is discussed in the text.

The term " partial branch block " is somewhat confusing because the complete cardiographic record obtained will be dependent upon conduction in both bundle branches. For example, if the left bundle branch is normal, then depressed conduction in the affected right bundle branch gives rise to the picture of various degrees of incomplete right bundle branch block as originally discussed from the experimental and clinical cardiographic viewpoints by Wilson and Herrmann (1920). If both the bundle branches have similarly depressed zones of conductivity, the P–R interval is prolonged and the QRS complex is of normal duration. If there is complete loss of conductivity in one bundle branch, for instance, the left, and depressed conduction in the other, the right, then as happened in the case reported herein, there is an increased P–R interval and complete left branch block.

Excellent illustrations of bilateral branch block have been published by Bain (1941), Case 3 in his article being of particular interest. Incomplete heart block is shown, the usual mechanism being a 2 : 1 heart block with right branch block, but occasionally two auricular beats are conducted in sequence, the second of which shows a prolonged P–R interval and a left, rather than a right, branch block. It seems reasonable to suppose in Bain's case that retarded conduction was present constantly in the right bundle branch, and when the left bundle branch conducted normally, right bundle branch block was manifest. However, when the left bundle branch was completely blocked, the right bundle branch conducted after a delay, resulting in an increased P–R interval and left branch block.

In the case reported herein it would seem a

justifiable assumption that the depressed zones of conduction in the bundle branches were associated with a pathological state in the upper part of the ventricular septum. Utilizing the conception of unidirectional block related to the orientation of slightly depressed to severely depressed zones in the bundles, as outlined by Herrmann and Ashman (1931), one might explain the observed conduction defects in the following way. The first excitatory processes to be conducted meet a severely depressed area in the right bundle branch which, however, is eventually traversed, while in the left bundle branch there is a slightly depressed zone above a severely depressed area and complete block in the left bundle branch occurs. A tenth of a second or so later, the left bundle branch has recovered, the excitatory process passes quickly through it, and a right bundle block complex appears. In general, it would appear that the right bundle branch conduction defect simulates type 1 A-V block while the left bundle branch conduction defect simulates type 2 A-V block as classified by Mobitz (1928), type 1 being a progressive increase in conduction time culminating in complete block, and type 2 being the sudden appearance of complete block without preceding increase in conduction time.

The possible relationship of the conduction disturbances to the clinical diagnosis of coronary insufficiency may be allowed if it be accepted that the blood supply to the conducting tissues were jeopardized. When normal sinus rhythm was present, there was never any auriculo-ventricular or intraventricular conduction defect. One might presume on a theoretical basis a further phasic decrease in blood supply during ventricular systole during which period the P wave that was to be followed by the bundle branch block QRS occurred. Such a supposition concerning the effect of systole on the blood supply to an ischæmic zone is the direct opposite to that proposed by Wolferth (1928) in explaining the A-V conduction in his case. If the phenomena observed were the effect of anoxæmic anoxia, the question of a possible elucidation of the problem from the work of Harris and Matlock (1947) arises. These investigators reported that the threshold of excitability was lowered and conduction rates increased in moderate anoxia while in severe anoxia the reverse effect was obtained. If the results were applicable to junctional tissues, one might explain the phenomenon of the sudden increase in conductivity and perhaps even an increase of excitability in the left ventricle in this case by assuming that a hypoxic environment changed from a severe state to a moderate one.

## Summary

A patient having intermittent sino-auricular block and interference dissociation was found to have also bundle branch block associated with the majority of the interference beats. The bundle branch block was either right or left, dependent upon the time relationships of the auricular beat to be conducted and the preceding R wave of the nodal (idioventricular) rhythm. The possibility of an intraventricular supernormal phase of recovery in conductivity in the left bundle branch might be utilized in explaining the phenomena, but it is not necessary if different recovery rates in excitation of the two bundle branches are hypothesized.

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# ELECTROCARDIOGRAPHIC STUDIES IN CRETINS

BY

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There is no direct method of estimating accurately the function of the thyroid gland; so other measures have to be employed in diagnosing thyroid deficiency and in regulating subsequent treatment. Recognition of typical cases of hypothyroidism should not be difficult, but there are borderline cases with slight symptoms that are not so easy to detect. Standard methods of investigation are helpful but have their limitations particularly in young children. At this early age, for instance, accurate estimation of the basal metabolic rate is difficult and therefore unreliable. The blood cholestrol level is usually raised in hypothyroidism, but the test may fail in early or mild forms of the disorder and other conditions may be associated with a high figure.

In searching for additional means of diagnosis attention has been drawn to certain electrocardiographic changes pointing to a disturbed action of the heart. This method of investigation has been used only to a very limited extent in children and pædiatric textbooks contain little or no information on the subject.

## Electrocardiograms in Hypothyroidism

In 1918 Zondek described cardiac disturbances in four adults suffering from hypothyroidism and on the basis of his observations introduced the term "myxœdema heart." The main changes he described were cardiac dilatation, a depressed heart action with a slow pulse rate but normal blood pressure, and the absence of the P and T waves in the cardiogram. After thyroid treatment all these abnormalities disappeared. Since then cardiographic investigations of this condition have continued, mostly in myxœdematous adults, but there have also been a few sparse references to children (Cori, 1921; Nobel *et al.*, 1924; Thacher, 1924; Doxiades and Pototzky, 1927; Fournier, 1942; and Sharpey-Shafer, 1943).

The changes generally reported are a low voltage curve with flat P and flat or negative T waves. Only two references can be found to alterations in the R–T segments. Chini (1929) reported two myxœdematous children in whom the segment had a convexity, "a tipo coronarico," similar to Pardee's original description in coronary sclerosis. Ohler and Abramson (1934) found similar changes in 4 of 21 adults with hypothyroidism. Prolongation of the P–R interval has been observed in isolated cases (Luten, 1920; Schittenhelm and Eisler, 1927; Ziskin, 1930; Davis, 1931; and Howard, 1929) and a lengthening of the QRS complex in others (Holzman, 1929).

Arrhythmias associated with myxœdema seem to be extremely rare. Solitary cases of auricular fibrillation and occasional premature contractions have been described (Ohler and Abramson, 1934; Guerrant and Wood, 1938; Willius and Haines, 1925; Walker, 1933; and Austin, 1937). Bradycardia of sinus origin or with complete heart block and the Stokes-Adams syndrome is sometimes encountered (Willius, 1925). Paroxysmal tachycardia is rarer still (Lisser and Anderson, 1931).

There is a general impression that abnormal electrocardiographic changes in myxœdema disappear in the majority of cases after some weeks thyroid treatment. Flattening of the P and T waves has been noticed after thyroidectomy designed to produce artificial myxœdema in the treatment of congestive heart failure and angina pectoris (Davis *et al.*, 1934) or when thyroidectomy has been carried out too liberally for Graves disease (Hamburger *et al.*, 1929). Animal experiments in support of this have not, however, produced constant results. (Burlage, 1922; Coelho, 1931; and Lueg, 1926).

## The Cause of Electrocardiographic Changes in Myxœdema

Various explanations have been given of the cause of these changes. An extra-cardial factor such as increased skin resistance has been one popular theory, but there is an increasing belief that an

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alteration in the heart and the conductive mechanism as a result of the hypothyroid state is primarily responsible.

*Cutaneous resistance.* In order to overcome the possible effect of skin changes in myxœdema, Nobel *et al.* (1924) used subcutaneous needle electrodes and found an increase in the height of the P and T waves compared to the tracing obtained with ordinary standard leads. From this they concluded that the skin and not the heart was primarily at fault.

Other investigators have not been able to confirm these observations and, furthermore, alteration of skin conductivity could hardly account for the prolonged conduction time and other abnormalities observed. The absence of cardiographic changes in skin diseases with extensive cutaneous thickening such as scleroderma and ichthyosis is also of some significance (Hallock, 1934). This has also been our experience in these disorders, in dermatomyositis, and with the widespread œdema of nephrosis.

Sherf and Boyd (1945) using a special electrocardiograph were able to measure the electrical potential directly from the heart. In myxœdema abnormally low potentials were recorded, indicating a lesion of the heart itself.

*Pericardial effusion.* Some authorities have attributed the cardiographic changes to a pericardial effusion which may arise in myxœdema. With thyroid treatment the accumulated fluid disappears and the cardiogram becomes normal, which might be advanced as further proof of the argument (Schnitzer and Gutmann, 1946). But on the whole these effusions are not common and we have never observed them in any child suffering from hypothyroidism.

*Nervous factors.* A decreased tone of the autonomic nervous system might influence the deflexions, especially of the T wave, but here again it hardly seems likely that this factor alone could produce the various other abnormalities. (Hamburger *et al.*, 1929; Ohler and Abramson, 1934; v. Pfaundler, 1938.)

*Anæmia.* Secondary anæmia, nearly always present in myxœdema, has been suggested as another possibility (Tung, 1931), but no comparable cardiographic changes have been found in other forms of anæmia of a similar degree of severity.

*Myocardial disturbance.* In advanced hypothyroidism there may be a reduced cardiac output and enlargement of the heart, which might well modify the shape of the T wave (Means, 1925; Sherf and Boyd, 1945), but similar cardiographic changes have been found in the early stages without any obvious cardiac failure (Ohler and Abramson, 1934). Myxœdematous swelling of the muscle fibres and connective tissue of the myocardium is the principal post-mortem change discovered, and it is this no doubt that produces the main effect on the cardiogram (Ord, 1880; Schultz, 1921; Ohler and Abramson, 1934; Misske, 1936; LaDue, 1945).*

Arteriosclerosis of the heart is quite common in adult myxœdema and could partly account for the cardiac disturbance (Fishberg, 1924; Christian, 1925; and Feldman, 1936). Coronary disease may thus be responsible for persistent alterations in the R–T segment or T wave deflexions occasionally remaining despite treatment (Ohler and Abramson, 1934; and Fournier, 1942).

## Present Investigations

The present investigation was carried out to ascertain whether electrocardiography can be of any diagnostic assistance in hypothyroidism in infants and young children, particularly when clinical evidence is doubtful. In the course of these studies we were able to place increasing reliance on the abnormal type of tracing discovered, to watch the cardiogram revert to normal under treatment, and ultimately to use it as a control of the optimum amount of thyroid required. Our studies were made on 24 cases, 6 boys and 18 girls, in whom either cretinism or myxœdema had been diagnosed, depending on the age of onset. Both are encountered in childhood, the one dating from birth but only becoming evident round about the third month, and the other appearing later in a previously healthy child. Myxœdema is relatively less common than cretinism; both were found to produce the same cardiographic picture.

The cases fall into two groups:—10 in whom a cardiogram was taken before thyroid treatment was begun and 14 who were already under treatment before this examination was made.

Details of the 10 untreated cases in the first group are summarized in Table I. Seven of them were under the age of one year when first examined. In their appearance all 10 showed typical signs of hypothyroidism with a protruding tongue, dry skin, thickened subcutaneous tissues, an umbilical hernia, hoarse cry, slow snaky movements, and constipation. A delayed bone age was found when radiological examination was carried out.

The electrocardiogram was abnormal in all cases, the most constant finding being a low voltage curve. In addition, changes in the R–T segment were noticed in 8 cases which we came to regard as characteristic. These changes appeared either as a

* See also Report of the Committee of the Clinical Society of London (1888) and for animal experiments (Goldberg, 1927).

TABLE I

TEN CRETINS. ELECTROCARDIOGRAMS TAKEN BEFORE TREATMENT WAS STARTED

| Case No. and sex | Date | Present age (years) | Clinical signs | Main electrocardiographic findings | Blood cholesterol (mg. %) | Total daily thyroid (grains) showing increasing dosage |
|---|---|---|---|---|---|---|
| 1 F | 12/9/47 | 2/12 | + + | Low voltage; R–T III abnormal | 214 | 0·2 |
| | 31/6/48 | 11/12 | — | Normal | | 1·0 |
| 2 M | 14/4/48 | 2/12 | + + | Low voltage; R–T I and II abnormal, T I and II negative | 216 | 0·5 |
| 3 F | 17/8/48 | 6/12 | + + | Low voltage; R–T I and R–T II abnormal | | 0·75 |
| | 7/9/48 | 7/12 | + | Q III deep, otherwise normal | 134 | 0·75 |
| 4 F | 29/10/46 | 6/12 | + + | Low voltage; R–T II abnormal, T I diphasic | 185 | 0·2 |
| | 15/7/47 | | — | Normal; left axis deviation | 160 | 1·5 |
| | 7/11/47 | 20/12 | — | Normal; left axis deviation | | 1·5 |
| 5 M | 25/3/47 | 6/12 | + + | Low voltage | 143 | 0·25 |
| | 1/4/47 | | + + | Same as 25/3/47 | | 0·4 |
| | 3/6/47 | | + | Q III deep, otherwise normal | | 0·75 |
| | 21/7/47 | | ± | Normal | | 1·5 |
| | 10/12/47 | | ± | Normal; left axis deviation | 174 | 1·5 |
| | 6/4/48 | 19/12 | ± | Normal | 176 | 1·5 |
| 6 F | 14/4/48 | 10/12 | + + | Low voltage; R–T II and R–T III abnormal | 188 | 0·5 |
| 7 F | 31/3/47 | 12/12 | + + | Low voltage; paroxysmal ectopic rhythm | | 0·75 |
| | 25/5/47 | 14/12 | + | Normal; left axis deviation | 146 | 1·0 |
| 8 M | 14/6/48 | 2 | + + | Low voltage; R–T II abnormal | 462 | 0·25 |
| | 17/7/48 | | ± | Normal | | 1·0 |
| 9 M | 22/7/48 | 6 | + + | Low voltage; R–T I and R–T III abnormal | 346 | 1·0 |
| | 30/7/48 | | + + | Voltage increased; R–T III abnormal, occasionally S–A block | 322 | 1·0 |
| | 10/8/48 | | + + | Normal rhythm. Same as 30/7/48 | | 0·5 |
| | 19/8/48 | | + | Voltage increased; R–T III abnormal | 333 | 1·0 |
| | 24/8/48 | | + | Same as 19/8/48 | 258 | 0·75 |
| | 30/8/48 | | + | S–T III almost normal | 190 | 1·0 |
| | 6/9/48 | | + | Same as 30/8/48 | 183 | 1·5 |
| | 21/9/48 | | ± | Same as 30/8/48; left axis deviation | 185 | 2·0 |
| 10 F | 18/3/47 | 8½ | + + | Low voltage; R–T II and R–T III abnormal | 246 | 1·0 |
| | 8/4/47 | | + + | Voltage increased; normal | | 1·0 |
| | 7/11/47 | | + | R–T II and R–T III abnormal | | 1·0 |
| | 6/1/48 | | ± | T III negative, otherwise as 7/11/47; low voltage | 200 | 1·5 |
| | 3/2/48 | | ± | R–T II and R–T III almost normal | | 2·0 |
| | 13/4/48 | 9½ | — | Normal | 164 | 2·5 |

sloping take off of the segment from the descending part of the initial complex or as a convexity of the segment. A negative T wave in standard leads I and II was recorded in Case 2 only.

Further cardiographic examinations were made during the course of thyroid treatment in 8 cases and the tracings were all found to revert almost or quite to normal in a relatively short time, in Case 3 for instance after 3 weeks treatment. Fig. 1 to 4 taken from Cases 3 and 8 are typical examples of the cardiographic changes and alteration in appearance of the children before and after treatment.

Arrhythmias were observed in two instances: ectopic paroxysmal contractions in the first record of Case 7 and sino-auricular block on one occasion during the course of treatment in Case 9.

Blood cholesterol was estimated in 8 cases before treatment was begun and was found to be above 200 mg. per 100 ml. in 5 and below this level in 3 cases.

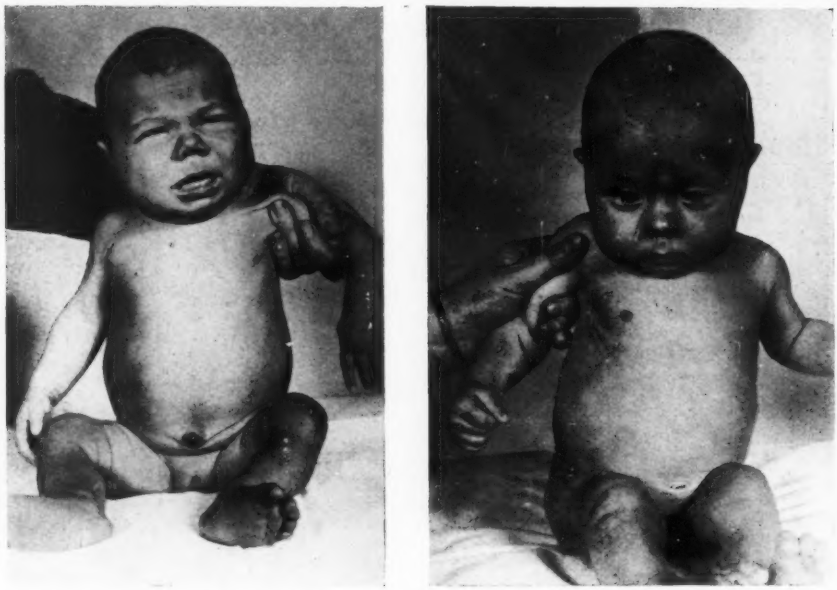

FIG. 1.—Appearance of the child (Case 3) before and after treatment with thyroid (0·75 grains a day) for two months.

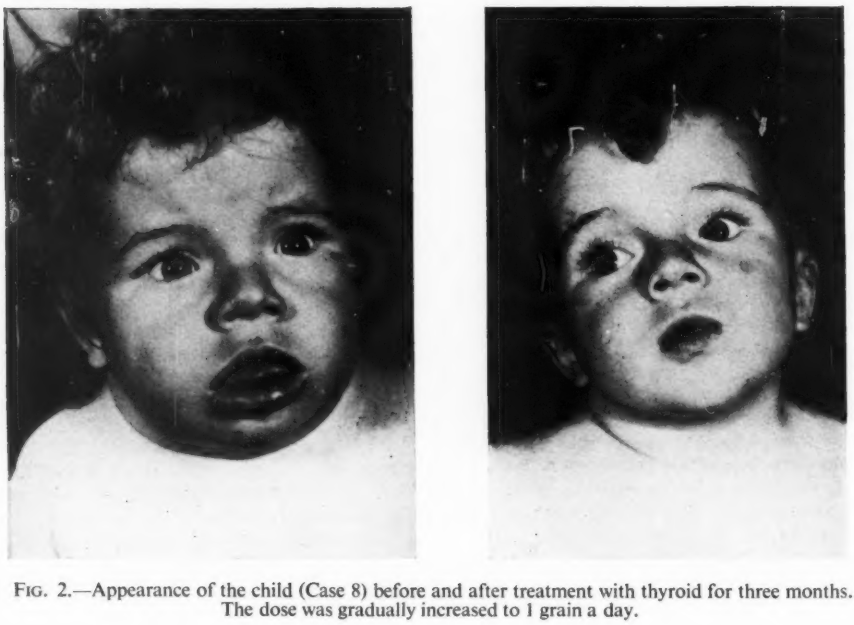

FIG. 2.—Appearance of the child (Case 8) before and after treatment with thyroid for three months. The dose was gradually increased to 1 grain a day.

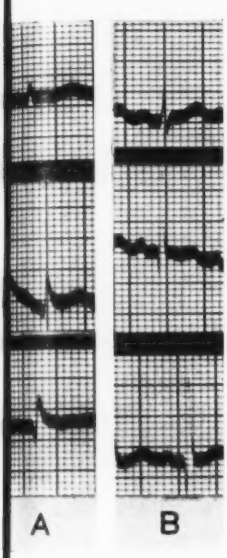


FIG. 3

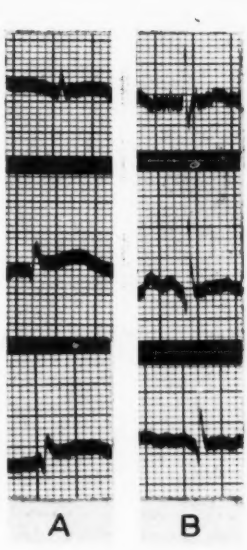


FIG. 4

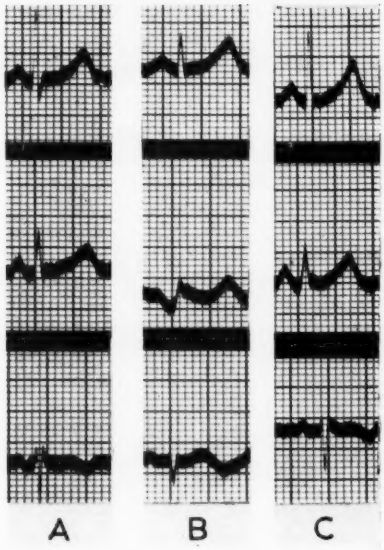


FIG. 5

FIG. 3.—Electrocardiograms of Case 3, aged 6 months. Standard leads. (A) 17/8/48. Before treatment. Low voltage curve and alterations in the S–T segments. (B) 7/9/48. Three weeks after treatment with thyroid (0·75 grain a day). Normal tracing.

FIG. 4.—Electrocardiograms (standard leads) from Case 8, aged 2 years. (A) 14/6/48. Before treatment. Shows the characteristic changes in cretinism. (B) 17/7/48. After treatment with thyroid for one month (dose gradually increased to 1 grain a day). Normal tracing.

FIG. 5.—Tracings illustrating insufficient thyroid dosage. Standard leads from Case 15, aged 10 years. (A) 19/2/47. Normal electrocardiogram after treatment with thyroid (3 grains a day). (B) 2/12/47. Changes appearing after decreasing thyroid to 2·5 grains daily for nine months. (C) 20/4/48. Electrocardiogram has again become normal after increase of thyroid to 3·5 grains a day for two months.

Data concerning 14 cretins in the second group are summarized in Table II. When first seen they all had the characteristic clinical appearance, but treatment had been started before the first cardiogram was taken and in 13 obvious signs of hypothyroidism had disappeared. The cardiogram was normal in 9 cases and in Case 12 the only change, a right axis deviation, was related to a congenital malformation of the heart which was a complicating factor.

### INSUFFICIENT DOSAGE OF THYROID

An abnormal curve was recorded at one period of our study in 4 children of this group (Cases 11, 15, 18, and 22) and in each instance this was found to be related to inadequate dosage of thyroid.

In Case 11 treatment was begun without delay but in inappropriate amounts, 0·1 grain daily for a month, subsequently reduced to 0·1 grain a week. At the age of 7 months when the child first came under our care she still had a cretinous appearance and the cardiogram showed the typical abnormalities already described. The blood cholesterol level, however, was not raised. Thyroid was then increased to 1·5 grains a day and the cardiogram became normal.

Case 15 was first seen at the age of 17 months, having been on a dose of 3 grains of thyroid a day for 3 months. A cardiogram taken at that time was normal. During the following years her hospital attendance was irregular and thyroid was reduced to 2·5 grains a day. We next saw her at the age of 10 years, normal in appearance, and we only realized that her thyroid level was sub-optimum when cardiograms in succession began to reveal a low voltage curve and changes in the R–T segments. The dose of thyroid was increased to 3·5 grains a day, whereupon the cardiogram again became normal (see Fig. 5A–C).

Case 18 had no obvious clinical symptoms beyond

TABLE II

FOURTEEN CRETINS. ELECTROCARDIOGRAMS TAKEN AFTER TREATMENT WAS STARTED

| Case No. and sex | Present age yrs. | Present age mths. | Thyroid therapy: Begun at yrs. | Thyroid therapy: Begun at mths. | Further Therapy: Date | Further Therapy: Daily dose (grains) | Electrocardiogram | Blood cholesterol (mg. per 100 ml.) |
|---|---|---|---|---|---|---|---|---|
| 11 F | — | 7 | — | 3 | 1/6/47<br>11/9/47<br>10/5/48 | 0·4<br>1·5<br>2·0 | Low voltage; inverted P III<br>Low voltage; inverted P III<br>Normal | 132<br>140 |
| 12 F | 1 | 6 | — | 6 | 15/4/48<br>29/7/48 | 0·5<br>1·0 | Right axis deviation; extra systoles<br>Normal rhythm | 165 |
| 13 F | 1 | — | — | 4 | 3/7/48 | 0·25 | Normal | 181 |
| 14 M | 1 | — | — | 8 | 20/1/47 | 1·0 | Normal | 169 |
| 15 F | 10 | 6 | 1 | 2 | 15/3/38<br>19/2/47<br>2/12/47<br>9/3/48<br>20/4/48 | 3·0<br>2·5<br>2·5<br>3·5<br>3·5 | Normal; left axis deviation<br>Inverted P III; left axis deviation<br>Low voltage; R–T II abnormal<br>Normal; left axis deviation<br>Normal; left axis deviation | 140 |
| 16 F | 2 | — | — | 8 | 5/1/48 | 1·5 | Normal | 206 |
| 17 F | 2 | — | 1 | 3 | 8/6/48 | 1·5 | Normal | 199 |
| 18 F | 3 | — | — | 3 | 15/6/48<br>27/7/48 | 1·0<br>2·0 | Low voltage; S–T II and S–T III abnormal<br>Normal | 220<br>161 |
| 19 F | 4 | — | — | 4 | 1/7/47 | 1·0 | Normal | 167 |
| 20 M | 4 | 2 | 2 | 4 | 2/7/48 | 1·0 | Normal | |
| 21 F | 5 | 3 | — | 9 | 3/6/47 | 2·0 | Normal | 196 |
| 22 F | 6 | 3 | 2 | — | 24/5/48<br>28/6/48 | 2·0<br>2·0 | Low voltage<br>Normal | 460<br>120 |
| 23 F | 8 | 4 | — | 7 | 16/7/48 | 1·5 | Normal | |
| 24 F | 11 | 2 | 1 | 5 | 15/9/47 | 1·5 | Normal | |

Only Cases 11 and 12 still showed a slight appearance of cretinism. Case 12 also had evidence of a congenital malformation of the heart. In Case 22 thyroid treatment had been omitted for one month when first investigated.

a slightly increased cholesterol level. Here again electrocardiography betrayed a subthyroid state and after 5 weeks increased dosage abnormalities in the cardiogram and blood cholesterol figure disappeared.

A similar sequence of events occurred in Case 22. Thyroid which was taken in adequate doses for four years had been omitted for one month. The cardiogram then taken showed a low voltage curve. The blood cholesterol was among the highest observed (460 mg. per 100 ml.) and yet there were no marked clinical features. The tracing as well as the cholesterol level became normal one month after resuming thyroid treatment at the same dosage.

Case 10 in the first group should also be included as a further example of inadequate therapy regulated by electrocardiographic control (see Fig. 6A–D).

Fuller details of these five cases will be found in Tables I and II.

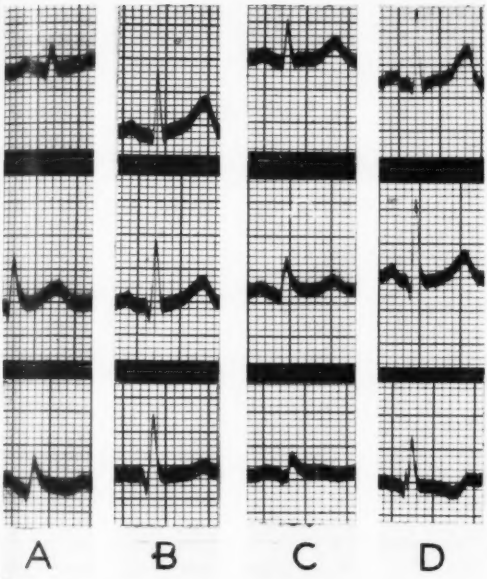


FIG. 6.—Tracings illustrating insufficient thyroid dosage. Standard leads from Case 10, aged 8 years.

(A) 18/3/47. Characteristic changes before treatment was started.

(B) 8/4/47. Normal tracing after thyroid, 1 grain a day for three weeks.

(C) 7/11/47. Seven months later. Thyroid dosage still 1 grain a day. The original changes have reappeared.

(D) 13/4/48. The thyroid dosage has gradually been increased to 2·5 grains a day for five months, and the curve is normal again.

### ELECTROCARDIOGRAPHIC ANALYSIS

The main data are summarized in Table III.

*Heart rate.* The average heart rate of the 10 untreated cretins was 107 a minute, the lowest figure being 91 a minute (Case 6). In fact no marked bradycardia was observed, but during the course of treatment the heart rate increased somewhat in all these cases. The greatest fluctuation occurred in Case 8 where the rate rose from 100 to 140 a minute after one month's thyroid administration. In the cretins under treatment the mean heart rate was 121 a minute, a figure in the upper limit of normal for this age.

*Sinus arrhythmia.* The degree of sinus arrhythmia was estimated by the method of Schlomka and Reindell (1936) and was found to be diminished in untreated cretins; in fact the heart beat in this condition, although slower in rate, was found to have the regularity of a " fœtal rhythm."

As a rule sinus arrhythmia become more evident during treatment and in the children who had been taking thyroid for some time before they came under observation it was within normal limits.

*Voltage deflexions.* Care was taken to standardize the string tension correctly (1 mv./1 cm.) before each tracing was taken and between each lead. The mean values of the various elements are shown in Table III and it is obvious that QRS and T deflexions are considerably smaller in untreated cretins than in healthy children. A negative T wave in lead III was seen in 8 cases, but by itself we do not regard this as abnormal and Hafkesbring *et al.* (1937) found it present in 40 per cent of healthy children.

TABLE III

LOW VOLTAGE ELECTROCARDIOGRAPHY DEFLEXIONS IN TWENTY-FOUR CRETINS

| | Standard leads | No. of cases | Average age (years) | Heart rate | P mv. | Q mv. | R mv. | S mv. | T mv. |
|---|---|---|---|---|---|---|---|---|---|
| Group I .. | Before treatment I | 10 | $2\frac{1}{12}$ | 107 | 0·04 | 0·05 | 0·34 | 0·13 | 0·14 |
| | II | | | | 0·10 | 0·12 | 0·58 | 0·03 | 0·17 |
| | III | | | | 0·05 | 0·15 | 0·44 | 0·01 | 0·05 |
| | After treatment I | 8 | $3\frac{6}{12}$ | 132 | 0·11 | 0·04 | 1·01 | 0·23 | 0·30 |
| | II | | | | 0·15 | 0·13 | 1·10 | 0·16 | 0·31 |
| | III | | | | 0·04 | 0·32 | 0·65 | 0·16 | 0·04 |
| Group II .. | After treatment I | 14 | $2\frac{6}{12}$ | 121 | 0·10 | 0·04 | 0·79 | 0·31 | 0·28 |
| | II | | | | 0·14 | 0·07 | 0·82 | 0·10 | 0·27 |
| | III | | | | 0·06 | 0·19 | 0·57 | 0·10 | 0·02 |

*Normal figures for comparison*

Average height of R (standard leads), normal infants: 0·7, 0·9 and 0·7 mv.; children of 3 years: 1·2, 1·5 and 0·8 mv. Normal height of T I and T II, in infants: 0·29 and 0·34 mv.; in younger children: 0·37 and 0·35 mv. (Nadrai, 1938, and Mannheimer, 1940.)

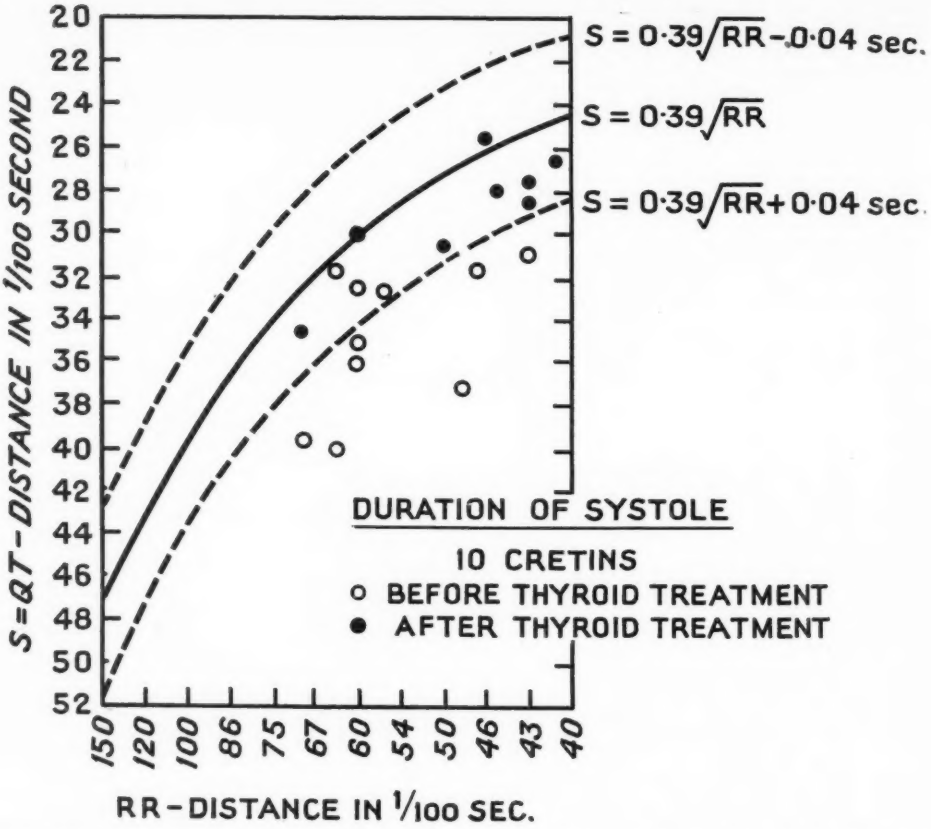


FIG. 7.—The duration of systole in 10 cretins before and after thyroid treatment. It was increased in most of the untreated cretins and became normal after thyroid therapy.

——— Mean values in normal subjects.
- - - - Normal range of variation.

During the course of treatment the low voltage curves disappeared and QRS and T resumed their normal shape and height fairly rapidly. This is also true of the P waves, particularly in lead I, although it should be realized that wide variations exist in normal children (Burnett and Taylor, 1936). The Q waves in lead III also tended to increase when thyroid was administered, but this was not seen in the first two leads.

In addition, left axis deviation appeared for a time in 5 cases. In fact it can become permanent and in one girl who has been under our care since infancy on regular and adequate thyroid therapy, left axis deviation is still present at the age of 17 years, although clinically and radiologically the heart appears normal and there is no evidence of left ventricular hypertrophy.

*P–Q and Q–T intervals.* The P–Q interval usually decreased slightly during treatment, the greatest change being from 0·16 to 0·12 sec. (Case 9). The mean values of the P–Q interval did not, however, show any obvious difference in the various groups included in Table III.

The duration of systole was calculated according to a formula suggested by Hegglin and Holzmann (1937). These authors have shown that normal values of the duration of systole (length of Q–T) plotted against the corresponding frequency of ventricular contractions (RR interval) will lie in an area on a graph limited by two lines and expressed

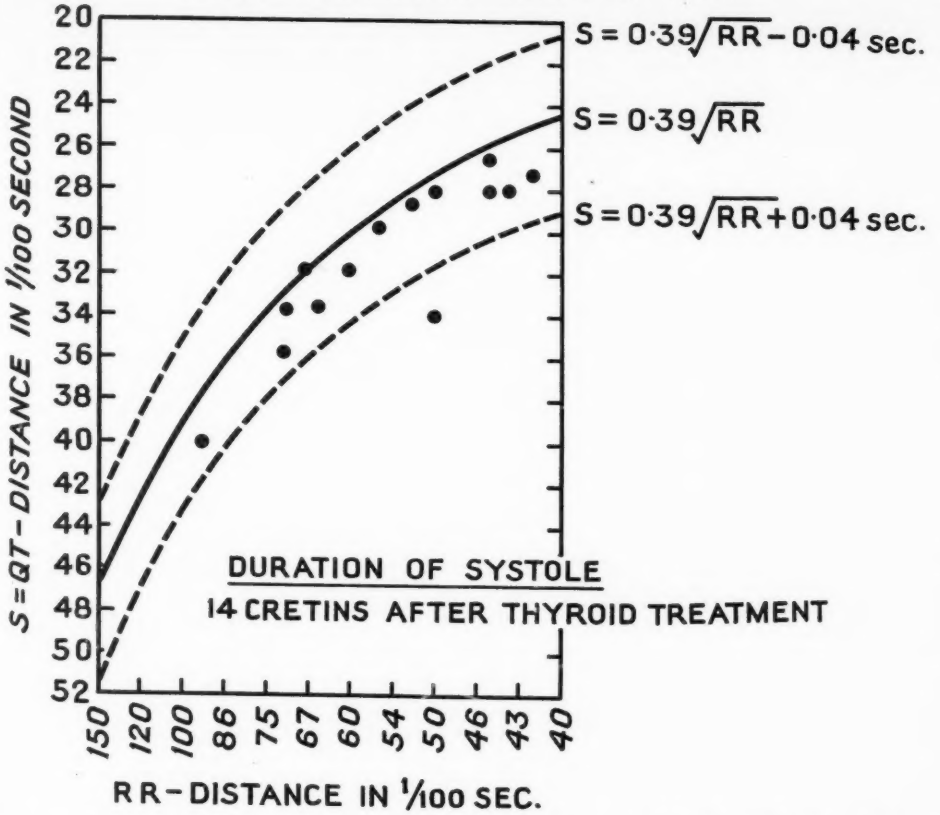


FIG. 8.—The duration of systole in 14 cretins after thyroid treatment. The figure shows that it was normal in all except one case of those cretins who had been treated with thyroid before the electrocardiogram was taken.

——— Mean values in normal subjects.
– – – – Normal range of variation.

as a mathematical formula, $0{\cdot}39\sqrt{\text{cycle}} \pm 0{\cdot}04$ sec. Using this method the length of systole has been plotted on a graph in the case of 10 cretins before and after treatment (Fig. 7).

The duration of systole was clearly prolonged in 7 cases before treatment and came within normal limits after thyroid had been given. A corresponding calculation was made in the 14 children who had already received treatment before cardiographic records were taken (Fig. 8). The duration of systole here was prolonged in only one instance.

### DOUBTFUL CASES OF CRETINISM

Occasionally cases arise in which an infant's appearance suggests cretinism but the absence of a completely characteristic clinical picture raises doubt in the diagnosis. In such circumstances we have found the cardiograph a great help.

Two cases can be quoted. An infant was brought to us with a large tongue protruding since birth and an umbilical hernia, but with no other clinical evidence of hypothyroidism. A tentative diagnosis of cretinism had been made which was rather shaken when the blood cholesterol was found to be normal (115 mg. per 100 ml.) and X-ray examination showed a normal bone age. A normal cardiogram was the deciding factor; a diagnosis of simple macroglossia was made, no thyroid administered and the child subsequently developed normally with a tongue reduced to the right size.

Another child was originally admitted to the hospital for seborrhœic eczema and gastro-enteritis.

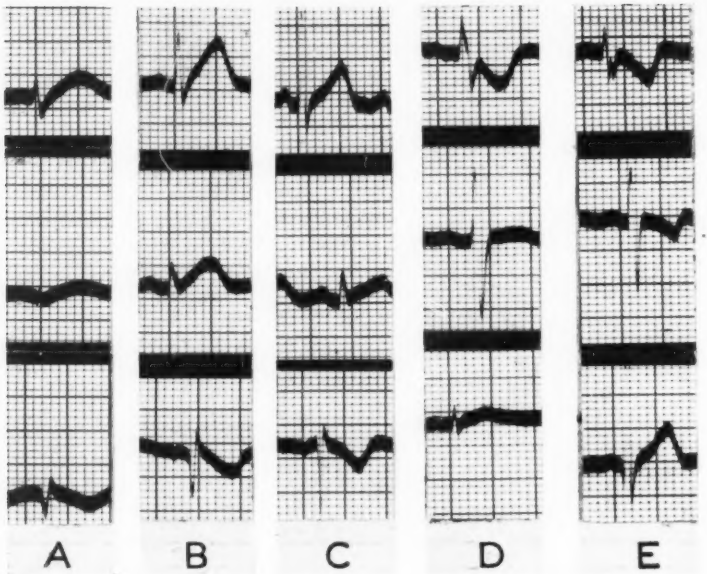


FIG. 9.—Electrocardiograms from Case 9, aged 6 years. (A) 22/7/48. Standard leads taken before treatment show the characteristic changes of cretinism. (B) 24/8/48. One month after treatment with thyroid (1 grain a day). Voltage increased, abnormalities in R–T segments disappearing. (C) 21/9/48. One month later, dosage of thyroid has been increased to 2 grains a day. Left axis deviation, otherwise almost normal tracing. (D) 30/7/48. Three unipolar chest leads taken one week after beginning of the treatment with thyroid (1 grain a day). Abnormal S–T segments in V 1; flat upright T in V 2 and low voltage curve in V 5. (E) 21/9/48. Three unipolar chest leads after two months treatment with thyroid (dosage gradually increased to 2 grains a day). S–T segment deviations in V 1 less marked; inverted T wave in V 2 and voltage increased in V 5.

The general appearance at that time also suggested a slight degree of hypothyroidism, a diagnosis also favoured by an increased blood cholesterol level. Thyroid therapy was given for four months, but when two early cardiograms in succession were found to be quite normal, treatment was stopped with no detrimental effect on the child's subsequent healthy development.

## DISCUSSION

These studies have shown that characteristic changes in the electrocardiogram occur in untreated cretins which are reversible in a comparatively short time on thyroid administration. If the dosage is interrupted or becomes inadequate cardiographic abnormalities reappear. Alterations in cutaneous resistance are probably partly responsible for the cardiographic changes because the voltage of the deflexions is considerably increased by the use of subcutaneous leads, a phenomenon we have also observed in normal subjects. Such myxœdematous skin infiltration can, however, only play a minor part. Changes in the R–T segment, which are also present in unipolar chest leads, and prolongation of systole could not be explained on this basis (see Fig. 9A–E).

Pericardial effusion, occurring at times in adult myxœdema, has not been encountered by us in cretins, and arteriosclerosis of the coronary vessels has not had time to develop at this age and cannot therefore be responsible for the R–T changes. Anæmia is also not a contributory factor; it is never profound and more than once the cardiogram was observed to return to normal during treatment without any corresponding improvement of the blood count. Nervous factors may have some effect on the cardiac action in cretins and the low degree of sinus arrhythmia present may be partly

an indication of this (Landtman, 1947), but from all the evidence direct involvement of the myocardium seems to be the most likely cause of the main cardiographic changes. Myxœdematous infiltration causes the heart muscle to swell and is likely to interfere with its action. Thyroid treatment rapidly restores the heart to normal and in this way the pathology is somewhat reminiscent of the heart in beriberi which quite rapidly becomes normal when appropriate treatment is given without delay (Weiss and Wilkins, 1937).


## Summary

Studies of the electrocardiogram were carried out on 24 infants or young children with hypothyroidism and the changes found are described. Evidence is brought forward of the value of this method of investigation in regulating the dosage of thyroid required and in the diagnosis of doubtful cases. The possible cause of these changes is discussed and evidence is produced pointing to direct myocardial involvement.


We are grateful to a number of our colleagues for placing their cases at our disposal and to Mr. Derek Martin and Mr. A. H. Prickett for their patient co-operation and technical assistance.

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# THE EFFECTS OF THIOCYANATE ON BASAL AND SUPPLEMENTAL BLOOD PRESSURES

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Despite the many conflicting reports published regarding the effect of thiocyanate on high blood pressure it has been shown (Alstad, 1948) that there were indications that in certain patients high blood pressure may be reduced by such treatment. Allusion was made to the impression that the fall was due to a reduction in both the basal and the supplemental pressure, taking basal to mean the pressure recorded after the removal of certain stimuli both intrinsic and extrinsic, and supplemental to refer to the part of the casual blood pressure that reflects the physical, emotional, and metabolic activity of the patient at the time (Alam *et al.*, 1943).

Thirty-two patients, selected because of a certain degree of hypertension, were investigated and were treated with potassium thiocyanate in doses varying from 0·3 to 0·9 g. daily, most of them for over nine months. The average age of the group was 56 years, twenty being over 50 years, and eight over 60 years of age. Females predominated over males, the ratio being 21 of the former to 11 of the latter. No patient was rejected because of complications of hypertension such as encephalopathy, angina pectoris, or previous cardiac failure. The casual pressures were recorded in a separate examination room after the patient had been recumbent for a few minutes; basal blood pressures were taken in hospital after a night's rest assured by hypnotics, as described by Kilpatrick (1948). During treatment blood was removed weekly for serum thiocyanate estimation until a desired level was obtained, thereafter the estimations were carried out at longer intervals.

The dose of a therapeutic agent varies from patient to patient and in such an investigation as this the drug must be used in an effective amount; hence the difficulty of determining a control series exactly comparable. To overcome this it was decided to attempt to control the patients against themselves, achieving this by replacing the drug with a placebo similar in appearance and in taste but containing no thiocyanate. This was done only after a significant fall in blood pressure had occurred, or after the patient had been treated for at least three months, that is, at a time when such a fall might have been expected. Care was taken to continue the routine of examination and blood sampling in a manner exactly comparable to that adopted when thiocyanate was being given. It was possible to arrange this control in 27 patients, the remaining 5 being omitted because of discontinuance of treatment due to change of location or of some complication of therapy. The results are shown in Table I.

## Basal Blood Pressure Reduction

The basal blood pressure, being recorded under conditions calculated to remove the effect of intrinsic and extrinsic stimuli, is probably a very reliable measure of the minimum pressure to which the cardiovascular system is subjected. It indicates the level to which the casual pressure may fall and is the guide to the fixity or lability of the hypertension according as the difference between it and the casual pressure is small or great. In the 32 patients examined an interesting relationship exists between the basal and casual pressures as shown in Fig. 1. Those patients with high casual pressure tend to have associated high basal pressure, indicating that an increase in the basal pressure is responsible, in part at least, for the high casual pressure in hypertensives.

Reduction of the basal blood pressure in any way, if produced by simple methods, would be of considerable importance to hypertensive patients. It is known that this may be effected by sympathectomy though not necessarily permanently. That a reduction may be produced in some cases by thiocyanate is seen from the fact that in 20 patients or 62 per cent, a fall in basal pressure of greater

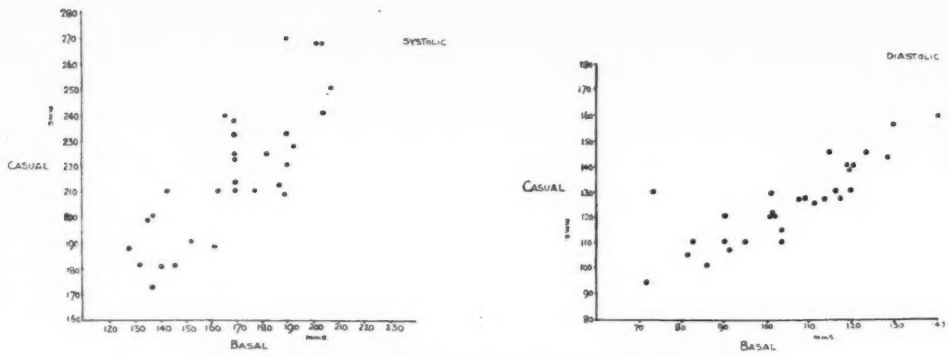


FIG. 1.—Relationship of initial basal pressure to initial casual pressure.

TABLE I

REDUCTION OF BLOOD PRESSURE IN THIRTY-TWO PATIENTS TREATED WITH POTASSIUM THIOCYANATE AND WITH A PLACEBO

| Case No. | Initial pressure | | | Reduction with treatment | | | Reduction with placebo | | |
|---|---|---|---|---|---|---|---|---|---|
| | Casual (CI) | Basal (BI) | Supplemental (SI) | Casual (CI−CT) | Basal (BI−BT) | Supplemental (SI−ST) | Casual (CI−CP) | Basal (BI−BP) | Supplemental (SI−SP) |
| 1 | 190/110 | 128/84 | 62/26 | 65/30 | 40/32 | 25/0 | 20/0 | +6/0 | 26/0 |
| 2 | 215/135 | 170/116 | 45/19 | 47/22 | 30/16 | 15/11 | 15/15 | 12/4 | 3/11 |
| 3 | 184/104 | 132/82 | 52/22 | 64/24 | 36/18 | 28/6 | 34/4 | 18/8 | 16/+4 |
| 4 | 232/128 | 170/106 | 62/22 | 52/20 | 24/10 | 28/20 | 32/16 | +4/+10 | 36/22 |
| 5 | 228/132 | 170/108 | 58/24 | 60/32 | 38/30 | 12/2 | 18/12 | 12/4 | 6/8 |
| 6 | 230/120 | 172/102 | 58/18 | 40/20 | 30/18 | 10/2 | 10/10 | +4/+4 | 14/14 |
| 7 | 180/110 | 142/94 | 38/16 | 40/22 | 20/20 | 20/2 | 30/16 | 6/6 | 24/10 |
| 8 | 240/124 | 210/112 | 30/12 | 65/24 | 28/12 | 30/12 | 18/4 | 0/+6 | 28/10 |
| 9 | 188/108 | 160/90 | 28/18 | 44/20 | 30/16 | 14/4 | 18/0 | 4/+2 | 14/2 |
| 10 | 213/130 | 142/74 | 71/56 | 63/40 | 22/14 | 41/26 | 43/40 | 8/2 | 35/38 |
| 11 | 210/140 | 176/122 | 34/18 | 40/30 | 28/10 | 12/18 | 10/10 | +4/+6 | 14/16 |
| 12 | 225/163 | 183/131 | 42/32 | 35/33 | 47/39 | 0/0 | 14/19 | 4/0 | 8/17 |
| 13 | 254/140 | 204/120 | 50/20 | 44/30 | 18/18 | 26/12 | 22/10 | +6/0 | 28/10 |
| 14 | 235/140 | 190/120 | 45/20 | 45/20 | 44/18 | 1/2 | 5/8 | 6/0 | +1/8 |
| 15 | 230/130 | 168/120 | 62/10 | 70/40 | 36/30 | 34/10 | 36/10 | 14/0 | 12/10 |
| 16 | 241/137 | 163/85 | 78/52 | 42/37 | 41/13 | 1/24 | 7/15 | 5/+5 | 2/20 |
| 17 | 170/131 | 137/100 | 33/31 | 41/43 | 15/12 | 26/31 | 20/36 | +3/6 | 23/30 |
| 18 | 185/110 | 141/92 | 44/18 | 41/20 | 25/10 | 16/0 | 20/0 | 1/6 | 19/+6 |
| 19 | 193/128 | 153/114 | 40/14 | 33/18 | 17/12 | 16/6 | 13/10 | +3/+2 | 16/12 |
| 20 | 185/120 | 145/102 | 40/18 | 35/20 | 15/12 | 20/8 | 15/10 | 4/2 | 11/8 |
| 21 | 211/123 | 163/102 | 48/21 | 30/23 | 11/2 | 20/22 | 0/4 | 2/0 | 0/1 |
| 22 | 200/95 | 136/73 | 64/22 | 32/20 | 0/7 | 36/14 | 20/4 | 0/7 | 25/0 |
| 23 | 200/120 | 136/90 | 64/30 | 40/20 | 0/0 | 40/20 | 30/10 | +4/+4 | 34/14 |
| 24 | 239/125 | 171/107 | 68/18 | 29/22 | 17/5 | 12/10 | 9/12 | 3/3 | 8/8 |
| 25 | 275/146 | 186/114 | 89/32 | 35/10 | 14/12 | 12/8 | 9/6 | 0/0 | 8/8 |
| 26 | 220/120 | 192/106 | 28/14 | 30/10 | 18/2 | 12/14 | 10/0 | 2/0 | 8/2 |
| 27 | 231/130 | 193/115 | 38/15 | 20/10 | 0/0 | 23/14 | 10/10 | 0/2 | 13/8 |
| 28 | 242/121 | 227/125 | 15/0 | 21/9 | 0/3 | 0/0 | — | — | — |
| 29 | 209/120 | 185/115 | 24/5 | 20/10 | 8/0 | 2/6 | — | — | — |
| 30 | 234/117 | 189/104 | 45/13 | 24/16 | 16/5 | 18/0 | — | — | — |
| 31 | 263/145 | 217/127 | 46/18 | 30/15 | 13/23 | 14/0 | — | — | — |
| 32 | 265/161 | 199/140 | 66/21 | 9/10 | 14/12 | 0/0 | — | — | — |

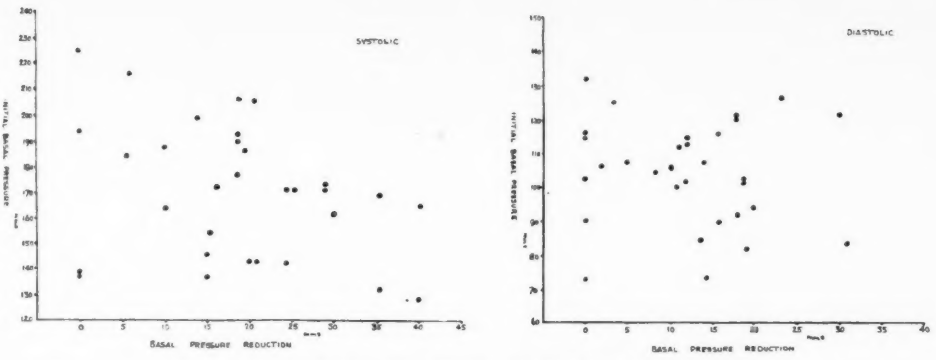


FIG. 2.—Relationship of basal pressure reduction to initial basal pressure.

than 15/10 mm. was produced. In 12 of these the reduction was greater than 25/15 mm. Falls in basal pressure less than 15/10 mm. were disregarded, for although work in this department has shown the basal blood pressure to be a physiological constant in normal individuals and in hypertensives to be much less variable than the casual pressure, it was felt that variations less than 15/10 mm. might come within the possible range of hypertensive fluctuation. The average fall was 25·8/15·7 mm. in the 20 cases mentioned while in the remaining 12 the average fall was 10/6 mm. If the fall in basal pressure is correlated with the initial basal blood pressure as in Fig. 2 there is an indication that the greater reductions tend to occur in patients with lower and moderate basal pressures. This tendency might be expected for one would anticipate high basal pressures in those with fixed hypertension and with more advanced pathological changes, and this is what obtained in this series as will be shown in another section.

With the use of a placebo the results were uniform no matter the extent of the reduction; the basal recordings with a placebo were similar to those before treatment commenced (cf. Fig. 3A). That the lowered basal pressure during treatment returned to within a few millimetres of its former level is taken to mean that the drug alone must account for the reduction, else with a placebo the pressure would not have returned consistently to the previous level. Had the basal pressure under the influence of a placebo not come back to the initial level (as will be seen occurred with the supplemental pressure) influences other than thiocyanate might have been responsible for the fall. There were three instances in which the reduction of basal blood pressure was maintained or returned very slowly to former levels even after thiocyanate was withdrawn completely for periods of up to three months during which no other treatment was given. Apart from the possibility of the initial readings not being truly basal, a simple explanation seems to be that the effect of thiocyanate in these cases greatly outlasted its presence in the blood. This prolonged effect has been noted by other investigators (Kurtz *et al.*, 1941; Fischman, 1948). Thiocyanate appears to act by altering some internal mechanism, an action usually operative during its administration only but which is sometimes protracted.

### SUPPLEMENTAL BLOOD PRESSURE

The supplemental blood pressure may be regarded as an index of the effect of various extrinsic stimuli acting on the patient at the time of recording. This part of the casual pressure has been shown by Smirk (1944) to be a variable independent of the basal pressure and accountable in the hypertensive for about one half of the increase above normal of the casual pressure (Smirk, 1944). With the removal of the excitatory causes as in sleep or with the conditions under which the basal pressure is recorded the supplemental pressure will approximate to zero at which level the blood pressure would, of course, be basal. That the supplemental pressure of a group of hypertensives would fall with any treatment, medicinal or psychological, might be anticipated as affecting the physical and emotional reactions of the patient. In the patients under observation the average supplemental blood pressure was 48/22 mm. or about the level already noted in studies on hypertensives conducted in this department (Kilpatrick, 1948). Under treatment the average supplemental pressure was reduced to 27/12 mm. The fact that, in all patients who were given a placebo, the supplemental pressure with it

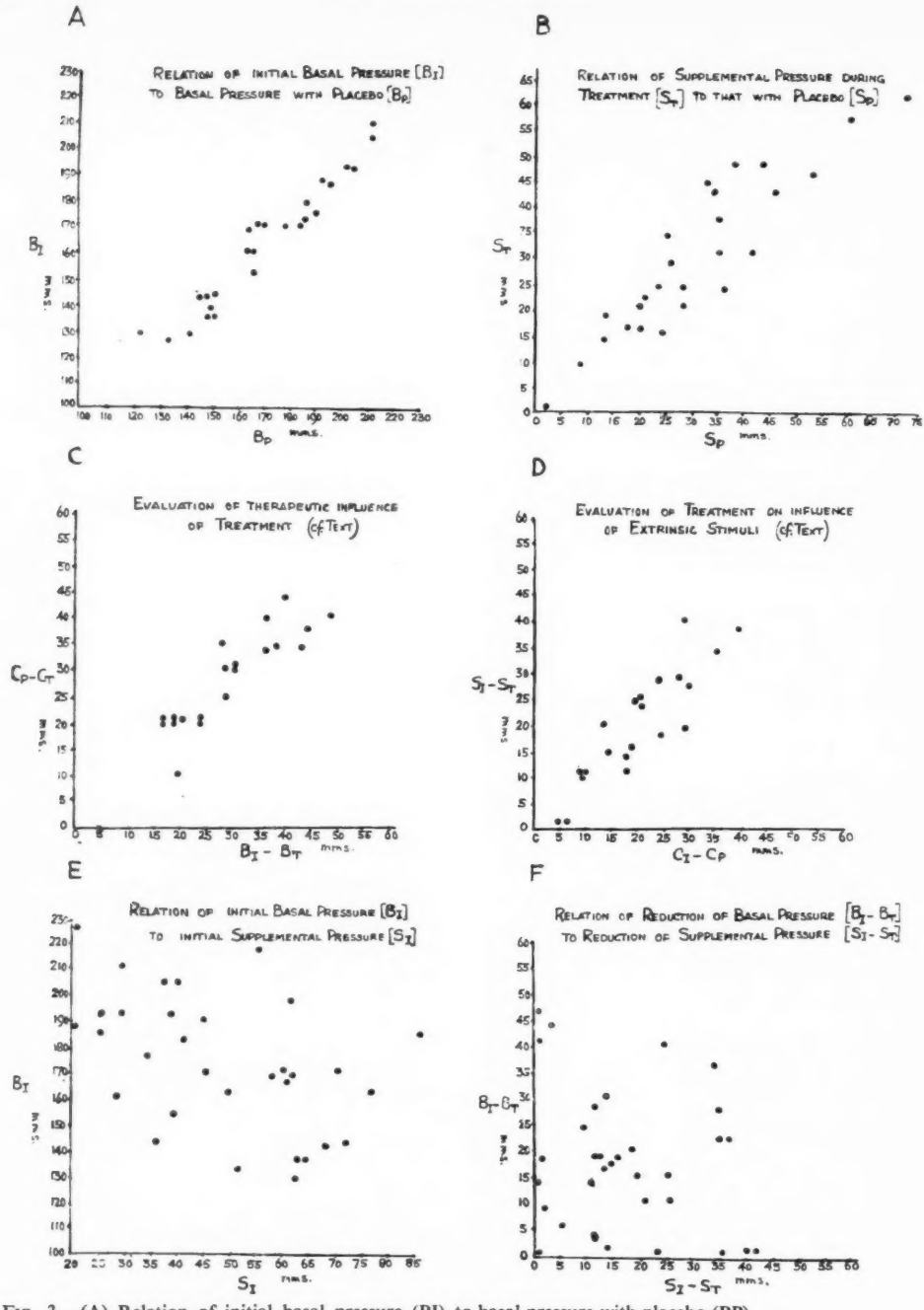


FIG. 3.—(A) Relation of initial basal pressure (BI) to basal pressure with placebo (BP).
(B) Relation of supplemental pressure during treatment (ST) to that with placebo (SP).
(C) Evaluation of therapeutic influence of treatment (of text).
(D) Evaluation of treatment on influence of extrinsic stimuli (of text).
(E) Relation of initial basal pressure (BI) to initial supplemental pressure (SI).
(F) Relation of reduction of basal pressure (BI–BT) to reduction of supplemental pressure (SI–ST).

approximates to that during treatment (cf. Fig. 3B) indicates that the reduction affected in supplemental blood pressure is a psychological one, for one could not expect an alteration in the influence of emotional stimuli when the patient is unaware of any change in the regime or medicine. If the effect were otherwise the supplemental pressure would be greater with a placebo than with the use of thiocyanate. The supplemental pressure fall in those patients with no significant alteration in basal pressure represents the total effect of thiocyanate therapy and therefore is due only to the psychological effect of treatment. The psychological effect of thiocyanate therapy therefore may be estimated by the difference between the initial supplemental pressure (SI) and that with a placebo (SP). This measure of the influence of thiocyanate in the supplemental pressure as opposed to its effect on the basal pressure may be shown arithmetically to equal the difference between the initial casual pressure (CI) and the casual pressure with a placebo (CP) since the casual pressure by definition is the sum of the basal and supplemental pressures, and as the basal pressure under treatment and with a placebo is the same. The relationship in this series between the differences of the initial casual and supplemental pressures and those with a placebo, CI–CP and SI–ST, respectively, is indicated in Fig. 3D in those patients whose reduction in pressure was significant, the formula CI–CP allowing of a more direct estimate of the psychological influences of treatment of patients in whom, for any reason basal recordings are unobtainable. Again as the supplemental pressure with thiocyanate and with a placebo have been shown to be approximately the same (cf. Fig. 3B) it follows (because the casual pressure is the sum of the basal and supplemental pressures) that the measurement of the direct effect of thiocyanate (BI–BT) will be the same as the difference between the casual under treatment and with a placebo (CP–CT) so allowing of a measurement of this influence without the necessity of having recordings of the basal blood pressure. That this relationship is present in this series is seen by scrutiny of Fig. 3C. These relationships are present only when there is a significant fall in pressure with treatment.

When the relationship of the initial basal and supplemental pressures is regarded (cf. Fig. 3E), it will be seen that there is a tendency for higher basal pressures to be associated with lower supplemental pressures, e.g. of 10 basal pressures over 180 mm. 8 were associated with supplemental pressures less than 45 mm., while of 18 under 180 only 6 had associated supplemental pressures less than 45 mm. A possible explanation may lie in the fact that most of the patients whose basal blood pressure was over 180 mm. were those in whom pathological changes were more advanced and therefore the cardiovascular system would be less able to reflect the effects of extrinsic stimuli. Smirk (1944) found the basal and supplemental pressures were substantially independent variables in a group of patients with essential hypertension selected for the absence of congestive heart failure and other complications. Kilpatrick (1948) showed that when heart failure occurred the supplemental pressure was reduced in greater degree relative to the basal. It is not surprising, therefore, that in the present series of cases including both groups that some of the more advanced hypertensives with heart failure or impending failure have lower supplemental pressures.

It would be likely, as the effect of thiocyanate on the supplemental pressure is independent of the effect on the basal that the reduction effected in the former would bear no relation to that produced in the latter; this is indicated in Fig. 3F which shows the basal pressure reduction plotted against the fall in supplemental pressure.

It would appear, therefore, that the effect of thiocyanate therapy on hypertensives in reducing blood pressure is a direct one as measured by the fall in basal pressure and also an indirect one as measured by the reduction in supplemental pressure, the combination of influences being responsible for the alteration produced in the casual blood pressure.

At this juncture one may conveniently regard the blood pressure reductions in the light of the extent of pathological change evident in the patients examined. All the patients in this series showed evidence of pathological changes associated with hypertension, whatever the ætiology, and this may be because the average age was over 55 years. All patients except two had some degree of cardiac enlargement involving the left ventrical which was of the typical hypertensive shape; it was possible to classify the enlargement as minimal, moderate, and considerable. Electrocardiography showed left axis shift in all cases, with a varying degree of left ventricular strain in over 50 per cent, particularly in those with large hearts. As the retinal vessels are the only ones capable of direct examination it was largely on the basis of retinal vascular change that the following clinical classification of the patients depends. Four subdivisions seemed practicable namely:

*Group* 1. (a) Minimal retinal changes in the shape of tortuosity and mild arterial constriction. Slight or no cardiac enlargement. Left axis deviation.

*Group* 2. (b) Moderate retinal changes, tortuosity, vascular constriction and nipping of the

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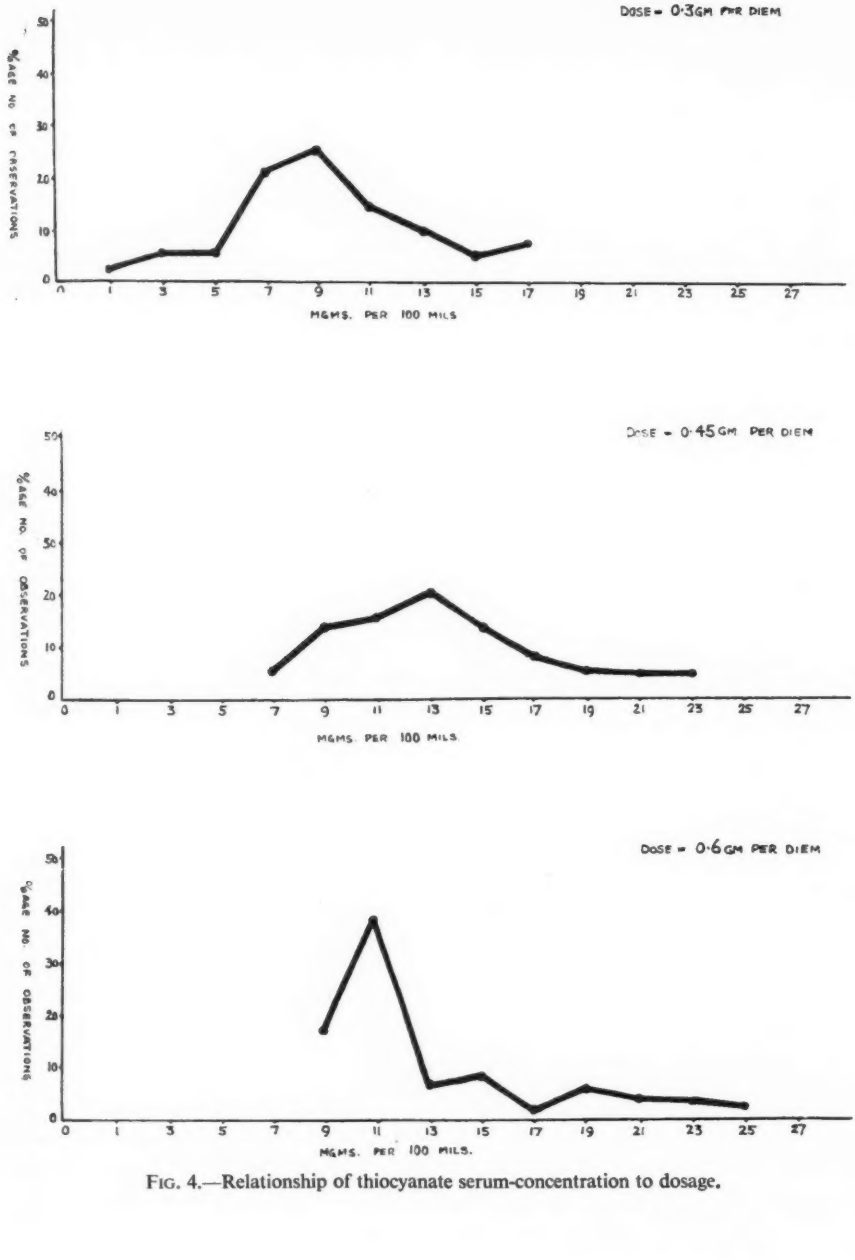
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FIG. 4.—Relationship of thiocyanate serum-concentration to dosage.

arteriovenous crossings. Moderate cardiac enlargement.

*Group* 3. (c) Marked retinal change but without papilloedema, hæmorrhage, or exudate. Cardiac enlargement usually moderate.

*Group* 4. (d) Marked retinal changes including hæmorrhage, exudate, and papilloedema. Cardiac enlargement usually considerable.

TABLE II

RELATION OF REDUCTION IN CASUAL AND IN BASAL BLOOD PRESSURE TO ASSOCIATED VASCULAR CHANGE IN PATIENTS WITH HYPERTENSION

| Clinical sub-division (see text) | Number of patients | No. showing reduction of Casual pressure of more than 40/20 mm. | No. showing reduction in Basal pressure greater than | |
|---|---|---|---|---|
| | | | 20/10 mm. | 15/10 mm. |
| Group 1 | 9 | 7 | 6 | 8 |
| Group 2 | 3 | 2 | 1 | 2 |
| Group 3 | 15 | 8 | 6 | 9 |
| Group 4 | 5 | 1 | 1 | 1 |
| Total .. | 32 | 18 | 14 | 20 |

It will be seen from Table II that reductions in casual blood pressure occurred in each group, but the incidence of reduction was greater in groups 1 and 2 than in 2 and 3. Indeed, out of 12 patients in the first two groups 9 had significant falls of casual pressure while in the latter two groups, 9 out of 20 patients showed any significant reduction in pressure. When the basal pressure reductions are viewed in the light of the degree of pathological change evident in the patients a similar distribution is seen. Thus it would appear that reductions in blood pressure tend to occur more easily in patients in whom the pathological changes associated with hypertension are least in evidence; such a conclusion is in keeping with the findings of Watkinson and Evans (1947) in this respect.

## DOSAGE AND BLOOD LEVELS OF KCNS

The dosage of the drug was a variable conditioned mainly in these patients by the response in blood pressure reduction. Experience had already shown that to start at a high dosage was to invite the onset of complications particularly in the form of rashes and gastro-intestinal upset, hence the initial dose was the moderate one of 0·3 g. daily. Blood levels were recorded at weekly intervals using Bowler's modification of Barker's technique (1944). If the blood pressure response were inadequate after four weeks the dose was increased by 0·15 g. daily. It was found that 0·45 g. was the dose usually necessary to produce a reasonable fall in basal and in casual pressure. If, however, such a fall did not occur the dose was again increased, in several instances to 0·9 g. daily. Generally the blood level followed the dose and larger doses were productive of higher serum concentrations (cf. Fig. 4). It was noted, that the lack of response in patients in whom no satisfactory fall of blood pressure was attained, could usually be attributed to the development of some complication of thiocyanate, e.g. rash or diarrhœa, early in treatment, in which case the drug was discontinued. Some patients did not have an appreciable fall in blood pressure despite large doses of drug and the attainment of high blood concentrations, e.g. over 20 mg. per 100 ml. Furthermore, in almost all patients in whom the pressure fall was adequate a dose of 0·45 g. daily was sufficient and this generally produced blood levels in the region of 8–12 mg. per 100 ml. (cf. Fig. 4). It would seem, therefore, that an adequate blood level must be maintained in the region of 10 mg. per 100 ml., which is best produced slowly, and that if the patient does not show a fall in blood pressure when the level is raised to this extent they are most unlikely to do so by attempting to raise it still higher. In several instances blood levels of over 25 mg. per 100 ml. were maintained for several weeks without producing a further fall in blood pressure.

Here one would remark that if a careful check is maintained on the serum level of thiocyanate and if the patient is seen frequently there appears to be little danger of untoward effects of therapy. Complications in this series were infrequent and took the form of rashes and gastro-intestinal upsets in four cases. In one only were mental symptoms encountered. As the average age in this series was 55 years it would indicate that age is no contra-indication to therapy.

## SUMMARY AND CONCLUSIONS

Selected patients with hypertension have been treated with thiocyanate over periods varying from one to twenty months. A reduction in basal blood pressure of more than 15/10 mm. was noted in twenty or 62 per cent of the patients. The greater reductions tended to occur with the lower or moderate blood pressures. This reduction in basal pressure has been shown to account for a proportion of the casual pressure fall and it has been suggested that the diminution in basal pressure represents the effective fall directly due to the therapy utilized, in this case, thiocyanate.

Indications have been given that the effect of the psychological influence of thiocyanate treatment may be measured by taking the difference in casual blood pressure initially and that occurring with a placebo, or by subtracting the supplemental pressure under treatment from the initial supplemental pressure. This latter measure of the psychological influence of treatment depending on the conception that the supplemental pressure is an index of the effect of physical, metabolic, and emotional stimuli of which, under the conditions of this investigation, the emotion was the principal factor. In addition, the therapeutic effects of thiocyanate might be gauged either by taking the difference between the basal pressure before and during treatment or by the difference between the casual pressure under treatment and with a placebo. This was shown to be expressed conveniently by the equation CI−CP =BI−BT where CI and CP respectively were casual pressure initially and with a placebo, and BI and BT were the initial basal and the basal pressure under treatment.

It has been shown that greater reductions are to be anticipated in patients in whom permanent pathological changes secondary to the hypertension are not advanced. The more these changes are in evidence as judged by heart size, electrocardiogram, and fundal examination, the less likelihood is there of any influence occurring with thiocyanate.

The following conclusions can therefore be drawn from this study.

The influence of potassium thiocyanate in reducing significantly the casual blood pressure in selected patients with hypertension is due to a diminution in both basal and supplemental pressure.

The reduction in basal blood pressure probably represents the direct effect of thiocyanate on the cardiovascular system.

The reduction in supplemental blood pressure with thiocyanate is a measure of the influence of this treatment in diminishing the effect of extrinsic stimuli on the patient, and is produced in a manner similar to the effect of a placebo.

The larger reductions in basal blood pressure are found in patients in whom pathological changes in the cardiovascular system are not advanced.

The optimal serum concentration of potassium thiocyanate is 8–12 mg. per 100 ml. which may be attained usually by a dose of 0·3–0·45 g. daily. Toxic effects are commoner with levels above this limit, but with care the serum concentration may be raised to much higher levels without complications, although it is not considered advisable to produce blood serum levels above 12 mg. per 100 ml.

If the desired effect of thiocyanate therapy is not produced by serum concentrations of 8–12 mg. per 100 ml. it is unlikely to occur by increasing the dose and the blood level.

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# RADIOKYMOGRAPHY IN PATENT DUCTUS ARTERIOSUS

BY

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The introduction of radiokymography dates from the pioneer work of Gött and Rosenthal (1912). The modern multiple slit kymograph was developed subsequently by Stumpf and his co-workers (1934), while later studies were made by Faber and Kjaergaard (1936) and Bordet and Fischgold (1937). In an earlier paper one of us (Wood, 1939) described the kymographic patterns that comprise the borders of the normal cardiac silhouette.

In the present study, X-ray kymography has been applied to the diagnosis of patent ductus arteriosus. The development during the past decade of the surgical treatment of the condition has greatly increased the importance of a diagnosis that may be difficult. In some cases the characteristic continuous murmur is not present and according to statistics quoted by Brown (1939) the pathognomonic murmur is absent in more than half of the cases. On the other hand Taussig (1947) claims that the diagnosis is based on the finding of a continuous murmur over the pulmonary area and that unless such a murmur is present the diagnosis cannot be made with certainty. It is when a murmur confined to systole is heard at the pulmonary area that diagnostic difficulties are likely to arise. Differentiation from pulmonary stenosis may not be easy and the possibility that patency of the ductus may be associated with other anomalies has to be remembered. It is an essential part of the diagnosis to exclude associated defects since when these exist ligature of a ductus may abolish an important compensatory mechanism. As exploratory operations are obviously undesirable, no effort must be spared to determine the correct diagnosis. We consider that the radiokymographic appearances which we now present should help to place the diagnosis of patent ductus arteriosus on a secure basis.

## Method of Investigation and Radiographic Technique

We have made radiokymographs in every patient in whom a diagnosis of patent ductus arteriosus was made or entertained. The majority of these later came to operation and in every instance the diagnosis was confirmed. The kymographs were all taken with the moving grid technique at a focus film distance of four feet. The grid used has a spacing of 11·5 mm. between the horizontal slits. At first, an exposure time of 3 seconds was used but later the rate of fall of the grid was increased to give an exposure of 1·8 seconds. At this speed satisfactory tracings were obtained with a heart beating at the normal rate, and also in patients with tachycardia.

Kymographs in the postero-anterior position were taken and these were supplemented by films in the oblique positions, especially the left oblique, whenever this appeared desirable. A standard exposure time was maintained so that the tracings made were comparable. This applied particularly where kymographs before and after operation were contrasted. The exposure factors were 65 KVP for children and as much as 90 KVP for full size adults, using 100 milliamperes with a rotating anode tube. In sixteen patients operation for ligature of the patent ductus was subsequently undertaken.

## X-Ray Appearances

The abnormality most commonly found in postero-anterior films of patients with patent ductus arteriosus is a prominence of the pulmonary arc and, in less degree, of the pulmonary conus. The cardiac outline may in other instances be entirely normal in patients proved at operation to have the same congenital defect. Taussig (1947) has referred to the slight prominence of the pulmonary conus in some normal children, and has insisted that the

diagnosis of patent ductus arteriosus should never be based solely on the contour of the heart. Consequently, the diagnosis must depend largely upon the murmurs unless other means are available, such as radiokymography.

The kymographic appearances of the left border of the cardiac silhouette in the normal heart may be summarized as follows. In the ventricular area waves of a certain type are seen; these consist of a curved upper limb due to the slow relaxation of the ventricle in diastole and a more horizontal lower limb representing the rapid contraction in systole. Above this is the zone of mixed or confused movements described originally by Stumpf (1934). This lies between the pulmonary artery waves above and those of the left ventricle below. The aorta and pulmonary artery show characteristic waves which have an almost horizontal upper limb due to lateral displacement by the pulse wave and a sloping lower limb representing the subsequent slower elastic recoil.

Light is thrown on the origin of the mixed movements by the kymograph shown in Fig. 1 which is taken from a man aged, 70, with complete heart block. There is one large ventricular wave recorded in the left ventricular area in each segment whereas at the lower part of the right border during the corresponding interval of time three distinct waves are seen which can only be ascribed to auricular contractions. In the segment immediately above the left ventricular region a further three waves can be seen of a similar rhythm which must also be auricular in origin and be ascribed to the left auricle or left auricular appendix which curves forward in this area at the root of the great vessels. This provides evidence that the left auricle may form part of the left border of the cardiac silhouette. It also shows that the mixed movements described must be partly auricular in origin, the other components being the super-imposed pulmonary artery waves. This zone of mixed movements must not be confused with the fine vibration waves described below, which lie in the ductus area between the aortic and the pulmonary artery levels.

### Kymographic Signs in Patent Ductus Arteriosus

In our kymographic study of sixteen patients with patent ductus arteriosus proved at operation, we have observed four special features of the left border of the cardiac silhouette. They are as follows.

(1) Para-aortic waves.
(2) Vibration waves.
(3) Exaggerated pulmonary artery waves.
(4) Exaggerated upper left ventricular waves.

Of these four signs the first two relate to the lesion itself while the last two are consequences of the hæmodynamic disorder caused by the defect. The features of each sign are described as follows.

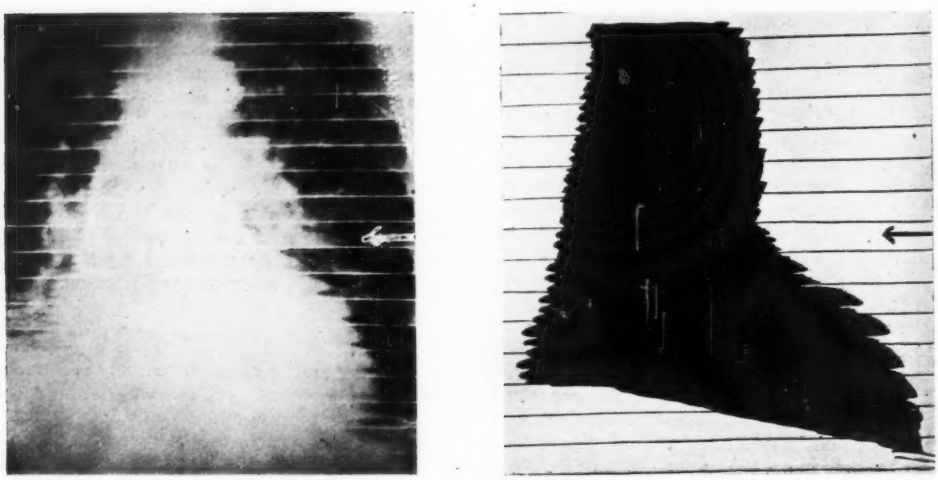

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Fig. 1.—Man, aged 70. Complete A-V block. (A) Kymograph. (B) Tracing showing auricular waves (marked by arrow) on left border of heart.

*Para-aortic waves.* These are wave forms which lie parallel to and lateral to the aortic knuckle. They are less dense than the shadow of the aorta, but are usually well seen when present as in Fig. 2. These waves differ from the zig-zag vascular shadows often seen well away from the mediastinum in the lung fields, which show transmitted pulsation from the aorta or left ventricle. This sign was present in six of our cases. It has been encountered in no other condition and we have never seen it in any kymograph taken after ligature of the ductus.

*Vibration waves.* These occupy a narrow region immediately below the aortic waves and blend farther down with the pulmonary artery waves. They are shown in Fig. 3 in which (A) shows the whole kymograph and (B) a magnification of the encircled zone in (A). The fine fibration waves of a frequency of approximately 400 a minute are seen at the centre of the magnified zone. Careful scrutiny is often required to detect these waves, by the naked eye in the kymograph. The reproduction in Fig. 4 shows ill-defined vibration waves, but the accompanying drawing made from the film by tracing the outline of the waves from the film, placed over a horizontal viewing box, illustrates them and their position. Fig. 5 shows a kymograph taken in the left anterior oblique position. The vibration waves are seen in the magnified section on the border of the ascending part of the arch of the aorta, a position that is surprising in view of the comparative remoteness from the ductus region. However, it is difficult to assign any other interpretation to these waves, which have been encountered on several occasions in left oblique films.

It is suggested that vibration waves constitute a visual radiological counterpart of the palpable clinical thrill, and that they are caused by the vibration of the ductus and the adjacent parts of the aorta and pulmonary artery. In some of our earlier kymographs, the zone of fine wave-forms was not well seen. This was due in part to the inherent difficulties of radiography in young children. With increased experience of the method and the subject better results were obtained and we have found the zone of fine wave forms to be a frequent feature of the kymograph in patent ductus arteriosus, being present in 12 of our 16 cases. Moreover, in kymographs taken after operative cure of the condition these special wave forms are no longer seen.

*Exaggerated pulmonary artery waves.* These are

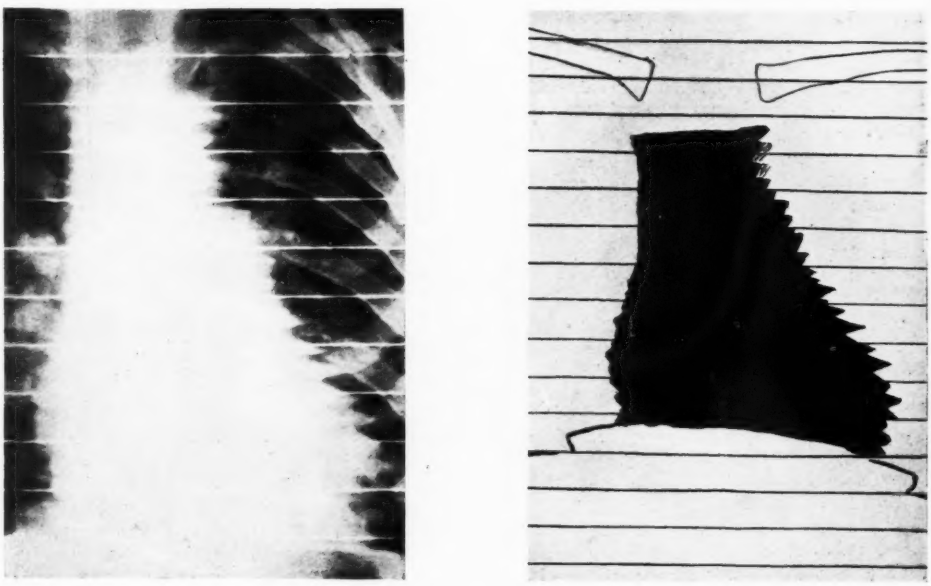

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FIG. 2.—Boy, aged 6. Patent ductus arteriosus. (A) Kymograph showing para-aortic waves. (B) Tracing of the kymograph: para-aortic waves shaded.

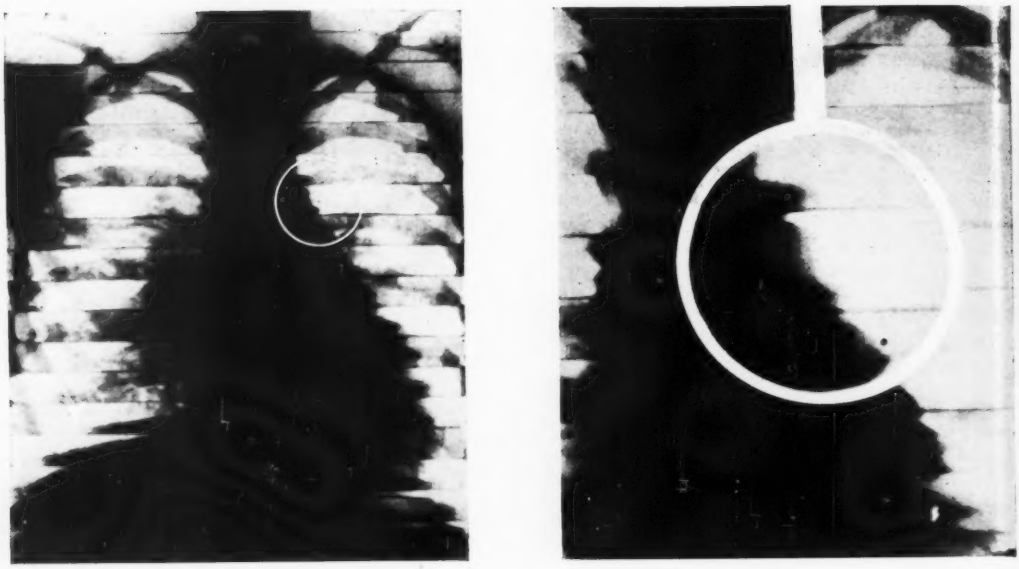

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FIG. 3.—Girl, aged 6. Patent ductus arteriosus. (A) Kymograph. (B) Magnification of encircled zone in (A) to show vibration waves.

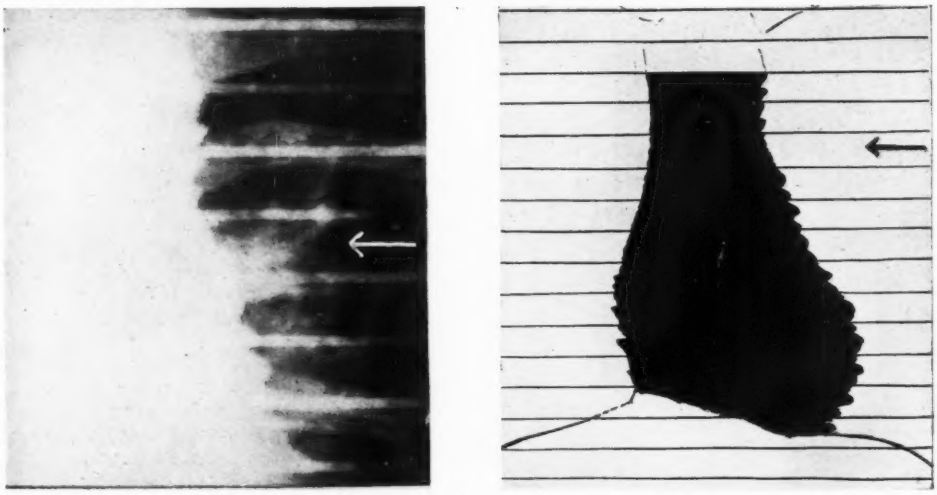

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FIG. 4.—Boy, aged 13. Patent ductus arteriosus. (A) Portion of kymograph showing ill-defined vibration waves. (B) Tracing of the whole kymograph to illustrate position (arrow).

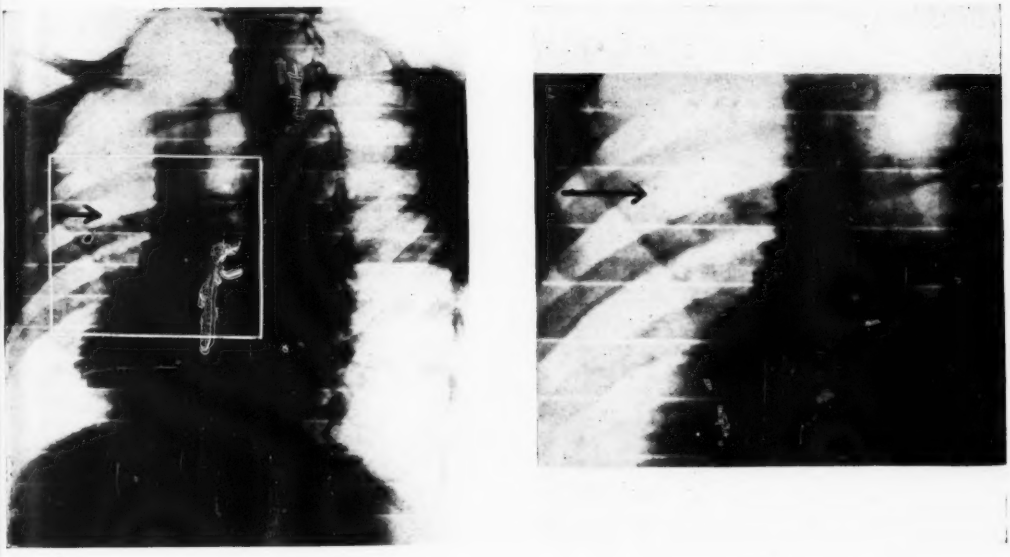

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FIG. 5.—Girl, aged 7. Patent ductus arteriosus. (A) Kymograph in left anterior oblique position. (B) Oblong marked area magnified to show vibration waves on border of shadow of ascending part of arch of aorta (arrow).

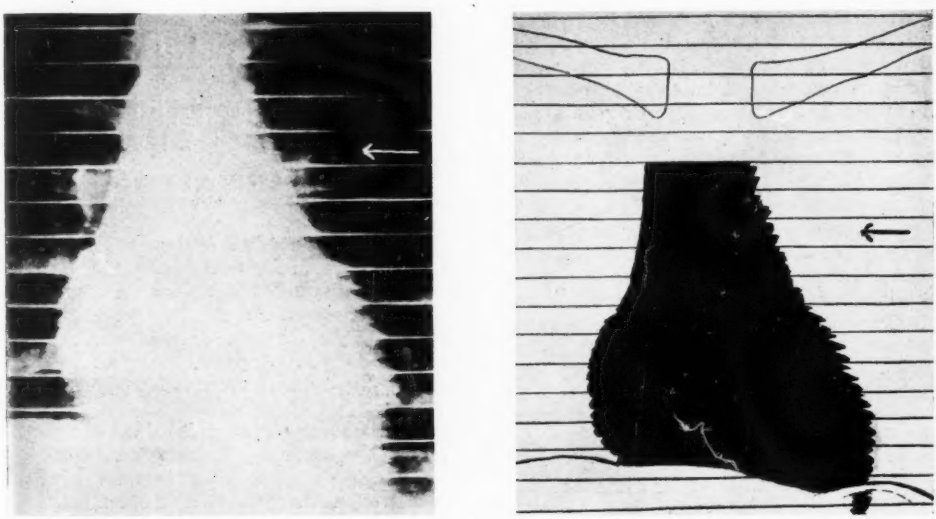

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FIG. 6.—Woman, aged 30. Patent ductus arteriosus. (A) Kymograph showing slightly convex pulmonary arc with exaggerated waves. (B) Tracing of kymograph to illustrate.

A B

FIG. 7.—Boy, aged 7. Patent ductus arteriosus. (A) Kymograph showing exaggerated upper left ventricular waves. (B) Kymograph of same patient after operation showing disappearance of the abnormally large waves.

shown in Fig. 6A in which the pulmonary arc is slightly convex. The accompanying drawing (Fig. 6B) illustrates the essential features of the kymograph. These appearances are in accordance with the prominent and pulsatile pulmonary arc frequently seen on radioscopy. The main branches of the pulmonary artery may also show exaggerated movement corresponding to the hilar dance so often seen on screen examination; this is of value in excluding pulmonary stenosis.

*Exaggerated upper left ventricular waves.* Fig. 7A shows very conspicuous wave forms due to the vigorous contraction of the upper part of the left ventricle. Such exaggeration is also seen in aortic incompetence. This is not surprising since both conditions involve a leak from the aorta and may therefore be expected to produce similar hæmodynamic disorders. After closure of the communication between the aorta and the pulmonary artery by ligation of the ductus, these abnormal ventricular contractions disappear, as is shown in Fig. 7B, a kymograph taken after operation.

## SUMMARY

Radiokymography has been applied to the diagnosis of patent ductus arteriosus. The series here presented comprises sixteen patients proved at operation to have this congenital defect. The following four kymographic signs are described.

(1) Para-aortic waves lying parallel to and lateral to the aortic zone.

(2) Vibration waves situated immediately below the aortic zone and between this and the pulmonary zone.

(3) Exaggerated pulmonary artery waves.

(4) Exaggerated upper left ventricular waves.

The production of these signs is discussed and reasons are given for relating the para-aortic and vibration waves to the ductus and the vibration in it and in adjacent structures. On the other hand, the amplification of the waves normally seen in relation to the pulmonary artery and the upper part of the left ventricle is due to the associated hæmodynamic disorder.

Reference is made to some of the difficulties in clinical diagnosis. It is considered that radiokymography is valuable in helping to establish conclusively the diagnosis before operation.

We wish to thank our surgical colleagues at the London Chest Hospital, especially Mr. T. Holmes Sellors, for their co-operation and help with the surgical data relating to the patients.

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# MASS MINIATURE RADIOGRAPHY IN THE DETECTION OF HEART DISEASE

BY

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The Glasgow Mass Radiography Unit began operations in the summer of 1944. Like other such units in the country, its primary intention was the early detection of tuberculous lung disease although it was realized that non-tuberculous conditions and notably heart disease would come within its sphere. The Mass Radiography Sub-Committee of the Minister of Health's Standing Advisory Committee on Tuberculosis, in 1943, laid down standards of cardiovascular abnormalities based on the appearances in full-size chest X-ray films taken after the miniature film had shown an unusual cardiovascular shadow. The abnormal appearances sought were general increase in size of the cardiovascular shadow, increased density of the shadow, displacement of the right cardiac border to the right and of the left border to the left in varying degree, and undue prominence of the large blood vessels.

It was soon observed that the postero-anterior large films gave little information that could not be given by the miniature film. The experienced eye could detect enlargement of the cardiac shadow in the miniature film, making allowance for the greater distortion at a distance of 36 inches from the X-ray tube focus as against 60 inches. Varying shades of increased density of the cardiovascular shadow itself such as may be caused by the enlarged left auricle of mitral stenosis could also be noted. Accordingly, it became the rule to offer full clinical examination to any person found to have an abnormality of the cardiac shadow on the miniature X-ray film.

During the initial period of our investigation some other observations were made. It was often seen, for example, that prominence of the pulmonary artery shadow did not indicate clinical heart disease. It was, therefore, decided to ask certain questions designed to bring out a history of previous rheumatic infection or of other illness significant in the ætiology of heart disease, and to discover the numbers of people passing through the unit who understood they had some form of heart disease. It was thought that if the X-ray appearances and history could be correlated the findings might be decisive in limiting needless recalls. Also, a history of known heart disease was frequently contradicted by the absence of cardiac abnormality on radiological or clinical examination.

After consideration of the experience of the unit in its first year of operation it was decided that the following groups should be recalled for full clinical examination: (1) patients with a history of rheumatic fever, chorea, or other illness suggestive of acute rheumatism, (2) those with a history of heart disease, and (3) those with abnormality of the cardiovascular shadow in the miniature X-ray film. It was hoped in this way to ensure the detection of cardiac abnormalities in patients unaware of an existing heart lesion with the minimum of inconvenience. This survey was begun in September 1945, and continued till March 1947, when the direct association of the authors in the work of the unit ceased. An account of the findings follows and certain conclusions are drawn; these should enable the unit, while pursuing its primary purpose of detecting tuberculosis in the community, to have a clearer understanding of the significance of the many cardiovascular abnormalities encountered in the day to day work of the unit.

## Age Distribution

Fully two-thirds of those examined were under twenty years of age and rather more than half under fifteen. The reasons for this distribution are the heavy concentration of the unit on the examination of school-leavers, and the choice for survey of industries in which there is a high proportion of young workers because the highest returns of active pulmonary tuberculosis can be expected in these

groups. As regards heart lesions, the expectation from such a distribution is that congenital disease and lesions due to acute rheumatism will predominate but not lesions the result of degeneration, hypertension, or chronic lung disease. The average recall rate for our purpose was about 49 per thousand; it was rather more in females and rather less in males mainly because of the larger recall rate in the well-represented group of girls under fifteen.

### Groups Recalled for Further Study

Table I shows the relative parts played by history of heart disease, abnormality of the cardiovascular shadow in the X-ray film, and rheumatic history in the recalling of examinees for clinical examination. It brings out that a finding of X-ray abnormality was the commonest single cause for recall, while a history of rheumatic illness and a history of heart disease were much less common causes.

TABLE I

Incidence of Abnormal X-ray Heart Shadow and a History of Heart Disease or Rheumatic Fever

| | |
|---|---|
| Total surveyed (both sexes) .. .. | 34,918 |
| Recalled for heart investigation .. | 1,703 |
| History of heart disease .. .. | 31% |
| Finding of X-ray abnormality .. | 66% |
| History of rheumatic illness .. | 44% |
| History of heart disease + finding of X-ray abnormality. | 11% |
| History of heart disease + history of rheumatic illness. | 19% |
| Finding of X-ray abnormality + rheumatic illness. | 19% |
| History of heart disease + finding of X-ray abnormality + history of rheumatic illness. | 7% |

The percentage figures refer to the number recalled.

It was also found that when a history of heart disease was not elicited, a finding of X-ray abnormality was a much more common cause for recall than a history of rheumatic illness. The reverse was the case in the group in which a history of heart disease was obtained.

### The Value of a History of Rheumatic Illness

Questions were put by trained clerical staff at the time of the miniature film examination to elicit a history of one or more attacks of rheumatic fever, one or more attacks of chorea or of other illness consistent with acute rheumatism. A preliminary investigation had suggested that histories of sore throat, blood-poisoning and scarlet fever were too common to be of value although if any one of these was accompanied by arthritis or muscular pains some importance might be attached to it. Such rheumatic symptoms are represented in this series under the heading of " other rheumatic manifestations." All histories were closely checked by the medical examiner at the time of the clinical examination and almost invariably found to be correct.

Table II shows the relative frequency of the various types and grades of rheumatic illness in this group. A single attack of rheumatic fever was the most frequent finding; other rheumatic manifestations were less common; chorea was relatively rare. There was no great difference between the sexes except that chorea was more common among the females.

TABLE II

The Incidence of the Various Grades of Rheumatic Infection in the Group Recalled on this Account

| | Male | Female | Both sexes |
|---|---|---|---|
| History of rheumatic fever once | 219 | 177 | 396 |
| History of rheumatic fever twice or more. | 36 | 35 | 71 |
| History of chorea once .. | 17 | 37 | 54 |
| History of chorea twice or more. | 1 | 7 | 8 |
| History of rheumatic fever and chorea. | 13 | 7 | 20 |
| History of other rheumatic manifestations. | 57 | 143 | 200 |
| Totals .. | 343 | 406 | 749 |

Table III shows the relationship in the whole series between a history of rheumatic infection and the clinical findings. It brings out the greater frequency with which acquired heart disease is associated with multiple attacks of rheumatic fever or chorea and the relative unimportance in respect of organic disease of the group of " other rheumatic manifestations." Equally noticeable is the frequency of normal findings when there is a history of a single attack of rheumatic fever.

In patients giving a history of rheumatic infection but not giving a history of heart disease there are few instances of acquired heart disease (21 out of 423 examined) suggesting that in most cases when acute rheumatism causes heart disease that fact is known to the patient. On the other hand, in patients giving a history of rheumatic infection and a history of heart disease the opposite obtains, namely, a high incidence of organic heart disease, and this is

TABLE III

SHOWS HOW A HISTORY OF RHEUMATIC INFECTION IS RELATED TO (*a*) NORMAL FINDINGS, (*b*) NON-SIGNIFICANT FINDINGS, AND (*c*) EVIDENCE OF ORGANIC DISEASE

| | Normal | Non-significant findings | Organic disease |
|---|---|---|---|
| History of rheumatic fever once. | 234 (54%) | 80 (52%) | 76 (52%) |
| History of rheumatic fever twice or more. | 23 (5%) | 12 (8%) | 32 (22%) |
| History of chorea once. | 30 (7%) | 11 (7%) | 12 (8%) |
| History of chorea twice or more. | 4 (1%) | 1 (1%) | 3 (2%) |
| History of chorea and rheumatic fever. | 9 (2%) | 3 (2%) | 8 (5%) |
| History of other rheumatic illness. | 130 (30%) | 46 (30%) | 16 (11%) |
| Total .. | 430 | 153 | 147 |

again most marked where there is a history of multiple rheumatic infection. Six cases of congenital heart disease and thirteen of hypertension were also discovered.

The group of non-significant findings such as innocent mitral systolic murmurs, or a split first sound at the apex would be expected to run parallel with the group of normal findings if it had no relation to rheumatic illness; if it had such a relationship it should reflect the results in the group of organic disease findings. Table III suggests that it has closer affinities with the normal group than with the group of heart disease.

### THE X-RAY APPEARANCES

The shadows on the 35 mm. film, being photographs of the appearances on a fluorescent screen placed at a distance of 36 inches from the focus of the X-ray tube, are somewhat distorted. Those placed to the periphery of the photograph are larger than those more centrally placed in comparison with the actual structures within the chest; and also in respect of the fact that tissues within the chest which are close to the X-ray focus, and therefore far from the fluorescent screen, cast larger images than those farther from the X-ray focus. Thus in ordinary postero-anterior films in which the patient faces the fluorescent screen with his back to the X-ray tube the shadow cast by the spine or a posteriorly placed tumour will be relatively broader than that of the aorta and that in turn relatively larger than the shadow of the heart or an anteriorly placed tumour. Further, cardiac enlargement will be emphasized and actual enlargement of the heart will never be quite so much as the shadow on the 35 mm. film would suggest. Another point is that prominences posterior to the heart will be emphasized at the expense of the shadows cast by the lateral borders of the heart so that the pear-shaped increase of density in the heart shadow cast by the hypertrophied left auricle in mitral stenosis will be more obvious than in a film taken at a greater distance than 36 inches.

Slight scoliosis may simulate cardiac enlargement in a miniature film and so may slight rotation of the patient. Films showing evidence of such deformity or of rotation were not included in this series. Table IV shows the frequency with which various radiological abnormalities were found.

TABLE IV

FREQUENCY OF X-RAY ABNORMALITIES IN THE SERIES

| | Male | Female | Both sexes |
|---|---|---|---|
| General cardiac enlargement. | 320 | 299 | 619 |
| Prominence of pulmonary artery. | 182 | 277 | 459 |
| Straightening of left heart border. | 41 | 74 | 115 |
| Unfolding of aorta .. .. | 42 | 45 | 87 |
| Broadening of base of heart.. | 18 | 50 | 68 |
| Prominent conus .. .. | 65 | 28 | 93 |
| Dextrocardia .. .. .. | 3 | 2 | 5 |

Table V shows the relationship between radiological general cardiac enlargement, irrespective of degree, and the clinical findings. It shows that in only a twelfth of the cases of cardiac enlargement without history of heart disease is there evidence of heart disease, and even where there is a history of heart disease the presence of a heart lesion in such cases is confirmed only in rather more than half the cases (about two-thirds of females, less than half of males).

The relationship between prominence of the pulmonary artery shadow in the miniature X-ray film and the clinical findings is shown in Table V. The pulmonary artery was judged to be prominent if it overlapped a line joining the aortic bulb and the left heart border at ventricular level. The Table shows that few cases with prominence of the pulmonary artery have an actual cardiac lesion; even in the group with a history of heart disease less than half have been confirmed as in fact having heart disease. The same conclusion can be drawn when the clinical findings are related to straightening of the left heart border in the X-ray film.

TABLE V

RELATIONSHIP OF X-RAY AND CLINICAL FINDINGS

| | Normal | Non-significant | Organic | Congenital | Hypertensive | Total |
|---|---|---|---|---|---|---|
| *Radiological Cardiac Enlargement* | | | | | | |
| No history of heart disease .. | 297 (72%) | 83 (20%) | 24 (6%) | 4 (1%) | 5 (1%) | 413 |
| History of heart disease .. | 29 (28%) | 14 (14%) | 55 (53%) | 3 (3%) | 2 (2%) | 103 |
| *Prominence of the Pulmonary Artery Shadow* | | | | | | |
| No history of heart disease .. | 305 (73%) | 96 (23%) | 14 (3%) | 3 (1%) | — | 418 |
| History of heart disease .. | 10 (24%) | 13 (32%) | 16 (39%) | 2 (5%) | — | 41 |
| *Prominence of Conus* | | | | | | |
| No history of heart disease .. | 24 (52%) | 15 (33%) | 6 (13%) | 1 (2%) | — | 46 |
| History of heart disease .. | 1 (4%) | 3 (14%) | 18 (82%) | 0 | — | 22 |

When broadening of the base of the heart shadow (i.e. the distance between the right border of the superior vena cava and ascending aorta on the right and the descending part of the aortic arch on the left) is related to the clinical findings, it is found that if it is present in association with heart disease the fact of the latter is known to the patient. No case of organic heart disease was found in this group in the absence of a history of heart disease. The same conclusion could be drawn when clinical findings were correlated with unfolding of the aorta, including prominence of the aortic bulb; as might be expected, hypertension was a more common finding in this group.

Table V also shows the relationship between prominence of the pulmonary conus and the clinical findings. When there is clinical evidence of disease and a prominent conus is noted in the X-ray film, the patient is usually already aware that he has heart disease. At the same time, the frequency of discovery of unsuspected organic disease was higher than with prominence of the pulmonary artery.

### THE CLINICAL EXAMINATION

The examination of 529 people who believed they had heart disease, revealed no evidence of this in 340 (64 per cent). Table VI shows this and also the incidence of cardiac lesions at different age groups. In almost all the cases the examination was entirely clinical, the findings in the erect position, in the supine position, on the left side, and after exertion being correlated. The blood pressure was taken if it was considered relevant. Only in exceptional cases were further aids to diagnosis, such as radiography in the oblique

TABLE VI

AGE DISTRIBUTION OF EXAMINEES AND INCIDENCE OF CARDIAC LESIONS IN THOSE WITH A HISTORY OF HEART DISEASE

| | *Age in Years* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Up to 14 | 15–19 | 20–24 | 25–29 | 30–39 | 40–49 | 50–59 | 60 and over | Total |
| Total number (A) (to nearest hundred). | 189 | 46 | 30 | 20 | 28 | 22 | 11 | 3 | 349 |
| Number with history of heart disease (B). | 247 | 61 | 35 | 28 | 69 | 38 | 41 | 10 | 529 |
| Percentage of (B) with heart disease. | 33 | 34 | 51 | 43 | 38 | 34 | 37 | 20 | 36 |

positions or following a barium swallow, electrocardiography or sphygmography, employed as it was the intention to interfere as little as possible with the routine of the school child or worker. Patients were on occasions admitted to hospital for diagnostic purposes or with a view to treatment.

The main clinical findings have been sufficiently considered in the preceding sections of this paper. It remains to discuss first the group of what has been labelled non-significant findings, and secondly, to give the details of our findings in the "organic disease" group. Under the heading of non-significant findings are such final clinical diagnoses as split mitral first sounds, innocent mitral systolic murmurs, split pulmonary second sounds and pulmonary systolic murmurs.

The total incidence of innocent mitral systolic murmurs, pulmonary systolic murmurs and split mitral first sounds, is shown in Table VII. Of the 1703 cases 798 were males, and 905 females.

*Split mitral first sound.* This is probably most commonly confused with the presystolic murmur of mitral stenosis. A split first sound was diagnosed in this series when no diastolic element was brought out by change in posture or by exercise; the sound was usually made more evident by exercise and was best heard at the end of expiration when the breath was held. As long as its possibility is kept in mind the very different character of the first part of the sound is not likely to be mistaken for a short presystolic murmur. In our series it was not commonly associated with X-ray abnormalities. Its incidence was 10 per cent in the absence of X-ray abnormality, and 7 per cent in association with such abnormality. It was no more common in patients giving a history of rheumatic fever than in those without such a history; the incidence was 8 per cent in both groups. These figures merit the belief that rheumatic infection played no part in the production of the finding. We are satisfied that the finding is not a significant one and that its incidence in such a series as this is as high as 8 per cent.

*Innocent mitral systolic murmurs.* The certain diagnosis of this group of murmurs is always difficult. Where a murmur did not have the properties possessed by the "organic murmurs," of loudness, propagation, and encroachment on the first sound, it was considered in the light of Evans' classification of innocent murmurs (Evans, 1947) and its relation to the patient's posture, and its position in the cardiac cycle, was studied. Phonocardiography was not used.

The incidence of the finding was between 5 and 6 per cent in both sexes. Its frequency was 5 per cent in the absence of a history of rheumatic infection and 6 per cent when there was such a history —figures so close as to show that rheumatic fever played no part in its causation. Among the group who had no reason to believe they had heart disease the innocent mitral murmur was found in rather less than 4 per cent whereas it was found in more than 9 per cent of those who believed they had heart disease. The innocent murmur was found in only 4 per cent of those with and in 8 per cent of those without, radiological abnormality. Stress should be laid, therefore, on the comparatively common incidence of this murmur, its frequent confusion with the "organic murmur," and the absence of

TABLE VII

SHOWS THE INCIDENCE OF MITRAL SYSTOLIC MURMURS, PULMONARY SYSTOLIC MURMURS AND SPLIT MITRAL FIRST SOUNDS IN THE PRESENT SERIES

| History of rheumatic infection. | None | | | | Rheumatic fever | | | | Other rheumatic manifestations | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| History of known heart disease. | No | | Yes | | No | | Yes | | No | | Yes | |
| | Absent | Present | Absent | Present | Absent | Present | Absent | Present | Absent | Present | Absent | Present |
| X-ray abnormality. | 22 | 729 | 130 | 73 | 200 | 85 | 178 | 86 | 17 | 121 | 33 | 29 |
| Total mitral systolic. | 4 | 24 | 13 | 7 | 9 | 3 | 19 | 7 | 0 | 5 | 3 | 1 |
| Total pulmonary systolic. | 3 | 76 | 7 | 8 | 13 | 5 | 16 | 4 | 1 | 18 | 2 | 2 |
| Total split mitral first sound. | 3 | 52 | 14 | 7 | 18 | 3 | 20 | 5 | 1 | 12 | 1 | 1 |

correlation with a history of rheumatic fever or X-ray abnormality.

*Split pulmonary second sound.* This finding is not uncommon in mitral stenosis. A split pulmonary second sound was found frequently in the series of 1703 cases examined and no significance could be attached to the finding at the time of examination. These cases are being followed up. The exact numbers in the series cannot be given because the great frequency of the finding was not fully appreciated at the start of the investigation and it was not particularly noted at first. Latterly, the prevalence of this sign in the absence of any discoverable clinical abnormality became obvious, and more recent observations have only served to confirm our opinion that it is particularly common and apparently without clinical significance. It was about twice as common in males and the incidence was comparable whether there was or was not an X-ray abnormality. It was almost twice as common when there was a " rheumatic history " and fully twice as common in those who understood they had heart disease.

*Pulmonary systolic murmur.* The murmur was found alone, or in combination with other non-significant findings, in 155 cases (9 per cent). No account is taken here of those cases in which it was heard in association with mitral stenosis. It was more common in females—almost 13 per cent as against 5 per cent in males. Rheumatic infection was not concerned in its production—8 per cent as against 10 per cent in the absence of such a history. While it was found in a considerable proportion of cases understood to have heart disease, fully 7 per cent in a total of 529, yet it was found more commonly among those who had no reason to believe that they had a cardiac abnormality (10 per cent of 1174 examined). It was more common in the presence of radiological abnormality than in its absence; the abnormality reported in almost every case was enlargement of the pulmonary artery, resulting in straightening of the left heart border or actual prominence of the artery beyond that line. Further, it was most common in the younger age-groups, e.g. of the 155 cases 110 were under 15 years. It was comparatively rare in adult life. The probable explanation of the presence of the murmur is that the artery is dilated beyond a normal pulmonary ring, and its more common occurrence in the younger age-groups may be associated with the greater distensibility of the soft and resilient artery in adolescence. Increase in the blood flow in the pulmonary artery as brought about by exercise accentuates a murmur already there and often brings out a murmur not heard previously. The importance and significance of this murmur must be recognized. Prominence of the pulmonary artery was much more commonly associated with it than with organic mitral disease.

### Organic Disease

Of the 1703 cases examined, 220 (just over 12 per cent) were found to have organic heart disease (Table VI). The bulk of these had mitral valve disease, a few had aortic valve disease, and the remainder were found to have auricular fibrillation, coronary occlusion, or myocarditis. Mitral valve disease was found in 185 (11 per cent); and aortic valve disease in 13 (less than one per cent); three patients had both aortic and mitral valve disease.

The incidence of normal findings among those believed to have heart disease has been stressed, but it should be noted that a diagnosis of organic valve disease was occasionally made for the first time in the course of the routine work of the mass radiography unit. Mitral valve disease was diagnosed in 41 cases and aortic valve disease in 3. Of the 41 with mitral disease 21 gave a history of previous rheumatic infection. Therefore, only 20, all of whom had abnormal X-ray findings, would have been found in the series relying solely on the lead given by the radiological picture. One only of the three patients with aortic disease was discovered because of X-ray abnormalities (in the other two there was a history of rheumatic infection). Twenty-one cases, therefore, of organic valve disease were discovered as the result of abnormal radiological appearances in 34,918 routine X-rays of the chest.

### Summary and Conclusions

In the course of the routine working of the Mass Radiography Unit in Glasgow many abnormal cardiovascular shadows were encountered. Of these the most common were general cardiac enlargement, prominence of the pulmonary artery, straightening of the left heart border, unfolding of the aorta, broadening of the base of the heart, prominence of the pulmonary conus, and dextrocardia. In an effort to limit needless recalls an attempt was made to correlate the various radiological abnormalities with a history of previous rheumatic infection or known heart disease.

Of 34,918 cases X-rayed by the unit in the course of the investigation, fully 67 per cent were under 20 years of age. Altogether 798 males (4·3 per cent) and 905 females (5·5 per cent) were recalled. Of the 1703 recalled the commonest cause of recall was an unusual X-ray picture; a history of previous rheumatic infection was a less common cause of recall, and least common was a history of known heart disease. All three reasons for recall were present in 115 cases (almost 7 per cent).

A history of one attack of rheumatic fever was associated with a finding of organic heart disease in, roughly, only one in five cases: two or more attacks resulted in clinical evidence of disease in rather less than half the cases giving such a history. This is a low incidence, but it must be realized that no strict check could be made on the accuracy of the history of rheumatic fever; many comparatively minor febrile illnesses masquerade under this heading. Although the numbers were smaller, it was found that one attack of chorea resulted in organic heart disease slightly more often than did one attack of rheumatic fever. Patients with a history of previous rheumatic infection and found to have heart disease mostly knew of it; apart from examples of hypertension only 23 cases were found to have heart disease not previously known to them—21 with organic valve disease, 2 with congenital heart disease.

Radiological cardiac enlargement was associated with organic heart disease in 93 cases (out of 516 in whom this X-ray finding was reported). Prominence of the pulmonary artery shadow was not a common cause of heart disease being brought to light for the first time; only 14 cases of acquired and 3 of congenital disease were found in this way out of 418 examined. Prominence of the conus, though less frequently diagnosed in the film, was more likely to be supported by clinical evidence of organic disease, than was a prominent pulmonary artery.

An outstanding finding was that no evidence of disease was found in 340 out of 529 patients who believed they had heart disease (64 per cent).

The frequency of non-significant findings such as split mitral first sounds, mitral systolic murmurs, split pulmonary second sounds, and pulmonary systolic murmurs is noted and their relationship with radiological abnormalities and a history of rheumatic infection described.

Of the 1703 cases examined 220 were found to have acquired organic heart disease; of these 185 had mitral disease, 13 aortic disease, and 3 both mitral and aortic disease. Only 41 cases of mitral disease and 3 cases of aortic disease were found in which the disability had been unknown to the patient. Of these, 20 with mitral disease and one with aortic disease were referred solely on account of the radiological findings. Thus only 21 cases of organic valve disease were diagnosed for the first time in 34,918 routine X-rays of the chest.

In conclusion the common radiological patterns sometimes thought to be suggestive of heart disease are not, as a rule, associated with clinical signs of disease. Such patterns by themselves do not suffice for a diagnosis of heart disease.

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# THE ELECTROCARDIOGRAM OF POSTERIOR CARDIAC INFARCTION

BY

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In suspected coronary artery disease, no clinical sign can as yet displace the electrocardiograph, which, by revealing past cardiac infarction, provides objective evidence for the diagnosis; much reliance must, therefore, be placed on the electrocardiographic signs of infarction. In lesions of the anterior wall, the signs are often characteristic, especially in chest leads. Posterior infarction is shown by deep and wide Q deflections, by significant R–T deviation, and by T inversion in lead II and III, and in the unipolar left leg lead. In the absence of coronary R–T changes, the signs of posterior infarction may be uncertain, since inversion of T in lead III, and occasionally also in lead II, may occur without infarction, and Q in lead II and III and in the unipolar left leg lead may be equivocal. The practical experience of diagnostic difficulties has led to the present study which is to show the close similarity of certain types of cardiograms representing posterior infarction to tracings taken from patients without infarction, and to examine records of infarction for additional electrocardiographic signs that might be helpful in the interpretation of equivocal curves.

The object of the analysis was the form of the QRS complex, in which changes due to infarction could be expected to last longer, and to be more specifically characteristic of this lesion, than changes in the T wave. In the absence of necropsy control, care was taken to include cardiograms only if the clinical diagnosis was firmly established. Patients with cardiac infarction gave a typical history of pain, and showed the classical changes of posterior infarction in the standard leads. With one exception (Fig. 3F), cardiograms were rejected if the signs of infarction were confined to the R–T segment and the T wave and did not include a small Q in lead III; if the cardiogram was equivocal, the diagnosis was accepted only if it was confirmed by serial tracings. Infarction was held to be absent if there was no history of pain and if the age and clinical condition provided no suspicion of coronary disease; in a number of cases, the clinical diagnosis was further supported by the presence of changes in serial cardiograms. Most of the tracings reviewed were taken in private practice with a Siemens electrocardiograph which registers time in 0·05 second; some of the patients were seen at the National Heart Hospital, under the care of Dr. William Evans. The records of 40 patients with posterior infarction were analysed.

## I. Electrocardiograms with Equivocal Changes of the QRS Complex in the Standard Leads

Of 40 patients with posterior infarction, 7 had standard limb leads with Q deflections in lead III, or II and III, which did not differ in size or depth or both from similar Q waves seen in patients without infarction. The cardiographic signs that caused uncertainty in the interpretation of the curves varied with the position of the long axis of the heart. In concordant cardiograms, showing mainly upright QRS complexes in the standard leads as seen when the heart was in the "vertical" position according to Wilson's terminology, Q II and Q III were of uncertain significance if they were less than 0·04 second in width and if the amplitude of Q III was less than 25 per cent of the tallest R in any limb lead. Cardiograms with a similar QRS pattern were seen in patients without infarction. In the tracings illustrated in Fig. 1 the infarct could not be recognized by the appearance of the Q waves or by any other change in the QRS complex; the presence or absence of S waves in lead I had no relation to the diagnosis, but Q I was more likely to be present when there was no infarction.

In discordant cardiograms, with QRS mainly upright in lead I and downward in lead III, Q was equivocal if it was deep, or deep and wide, in lead III, but small or absent in lead II. Care had to be taken to exclude a false Q III: when each successive beat in lead III was examined, a small R was often

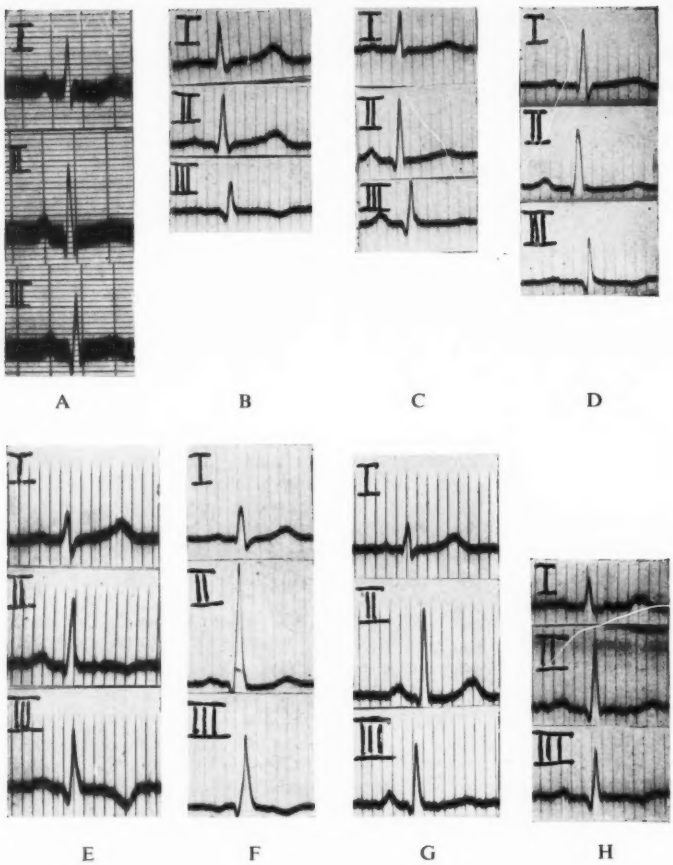


FIG. 1.—Electrocardiograms of the concordant type with equivocal Q deflections.

(A) Case 1: Man aged 45: posterior infarction (see also Fig. 4C).
(B) Case 2: Man aged 36: palpitation.
(C) Case 3: Man aged 77: broncho-pneumonia.
(D) Case 4: Man aged 47: palpitation.
(E) Case 5: Man aged 47: posterior infarction.
(F) Case 6: Man aged 31: left mammary pain.
(G) Case 7: Woman aged 21: extrasystoles.
(H) Case 8: Woman aged 57: thyroid toxæmia.

found to precede the downward deflection which, in many tracings, was then revealed as an S wave. The absolute size of Q III and its size relative to the R waves in other leads, was the same in patients with and without infarction; a wide Q III was more frequent in infarction (Fig. 2A and E) but also occurred in its absence (Fig. 6B); a Q I was again recorded more often when there was no infarction.

Deep inspiration decreased the size of Q III in most patients with infarction and in normal controls (Fig. 5 and 6). Infrequently, Q III was abolished by deep breathing in subjects without infarction (Fig. 5C and 6B). In infarction Q I was usually absent or small. If in individual patients Q I was shown before infarction, it was reduced in amplitude or abolished after the attack (Fig. 3); but when the cardiograms of all patients with posterior infarction were examined, Q I was found in 14 out of 40 records. The presence or absence of Q I was, therefore, of no diagnostic significance.

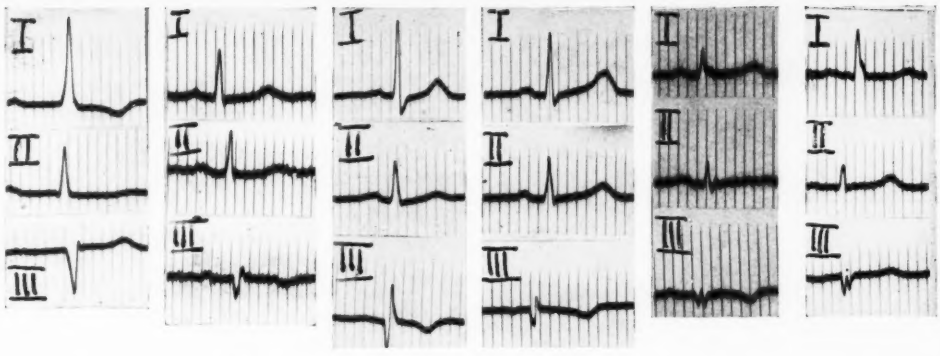


FIG. 2.—Electrocardiograms of the discordant type with equivocal Q deflections.

(A) Case 9: Man aged 67: hypertension and posterior infarction (ten years after the tracing shown in Fig. 3A).
(B) Case 10: Man aged 50: left mammary pain.
(C) Case 11: Woman aged 65: moderate hypertension.
(D) Case 12: Woman aged 37: extrasystoles.
(E) Case 13: Man aged 66: posterior infarction (one year after the tracing shown in Fig. 3H).
(F) Case 14: Woman aged 44: left mammary pain.

### II. Unipolar Limb Leads in Posterior Cardiac Infarction

Unipolar limb leads were analysed in 18 cases of posterior infarction. The leads were taken with the Wilson technique and then designated VR, VL, VF. In other cases, the Goldberger method was adapted to the central terminal of Wilson by detaching the indifferent limb electrode from the limb under exploration; the leads were then called aVR, aVL, and aVF. The left leg lead showed a deep and wide Q (with an amplitude of 30 per cent or more of the amplitude of R in this lead and with a width of 0·04 second or more) when Q II and Q III were also characteristic (Fig. 4). In cardiograms with discordant standard leads and equivocal Q waves, Q in the left leg lead was wide (Fig. 6A), but not always deep (Fig. 6D); in records of the concordant type with small Q waves in lead II and III, Q in the left leg lead was also small in width and size (Fig. 5A and D). In all cases of infarction, the Q wave, whatever its size, was deeper in lead III than in the left leg when allowance was made for augmentation in Goldberger leads. The voltage of Q in the left leg lead was reduced by deep inspiration.

All cases of posterior infarction showed an initial upright deflection in the left arm lead; it was more than 1 mm. in amplitude and often broad or slurred in the ascending limb. A monophasic upright deflection was recorded in some cases; others showed an S wave, but a small R followed by a deep S was not seen. In the right arm lead, the initial deflection was upright in 15 out of 18 cases and varied in amplitude from a small spike to a size of 4 mm.; an R wave in the right arm would be expected to show as a Q wave in lead I, but in all 15 cases Q I was either absent or smaller than R in the right arm lead after allowance was made for augmentation. When right bundle branch block was added to posterior infarction, the unipolar limb leads conformed to the infarction pattern (Fig. 4D).

### III. Unipolar Limb Leads in Patients without Infarction showing Cardiograms with Inconclusive Q Waves in the Standard Leads

Equivocal Q waves in the standard leads did not signify infarction if the initial deflection in the left leg lead was upright (Fig. 5C and 6B); in patients of this type, Q III was abolished by deep inspiration. In concordant cardiograms, a small Q in the left leg lead was as inconclusive as a small Q in lead II and III; it was not abolished by deep inspiration. Unlike the Q of infarction, Q VF was often of the same size as Q III (Fig. 5E and F). In these cases, the left arm lead also differed from the infarction pattern and showed an R wave of small voltage. If Q II and Q III were equivocal and the cardiogram conformed to the infarction pattern in lead VF and VL, a significant deviation might yet be shown in the relation of Q I to the right arm lead: in this case, Q I was of the same size as R in VR (Fig. 5B). In

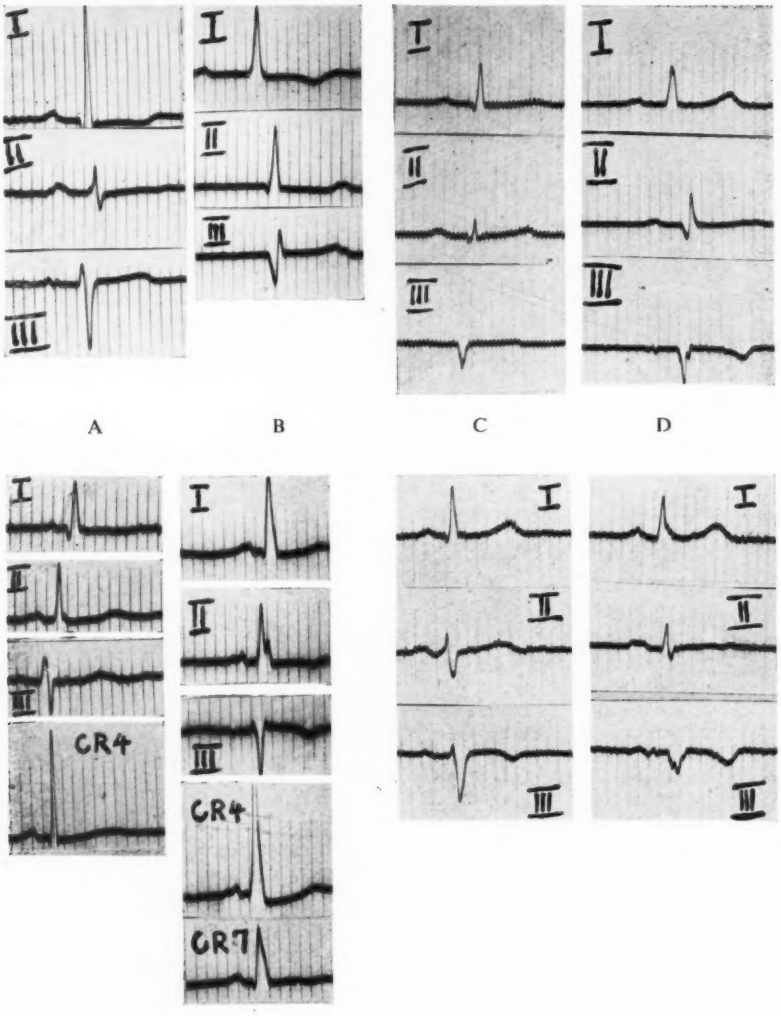


FIG. 3.—Electrocardiograms taken before and after posterior infarction.

(A) Case 9: Man aged 57: hypertension.
(B) The same: two years after infarction.
(C) Case 15: Man aged 58: angina of effort.
(D) The same: three weeks after infarction.
(E) Case 16: Woman aged 67: hypertension.
(F) The same: on day of infarction.
(G) Case 13: Man aged 65: angina of effort.
(H) The same: two months after infarction.

discordant cardiograms, Q in the left leg lead was less wide than the Q of infarction; it differed from the Q VF seen in the concordant type of tracing in that it was deep, yet smaller than Q III, even in the absence of infarction. An initial downward deflection in the left arm lead occurred only in patients without an infarct (Fig. 6E).

It was concluded that equivocal Q waves in the standard leads did not indicate posterior infarction if in unipolar limb leads the initial deflection was

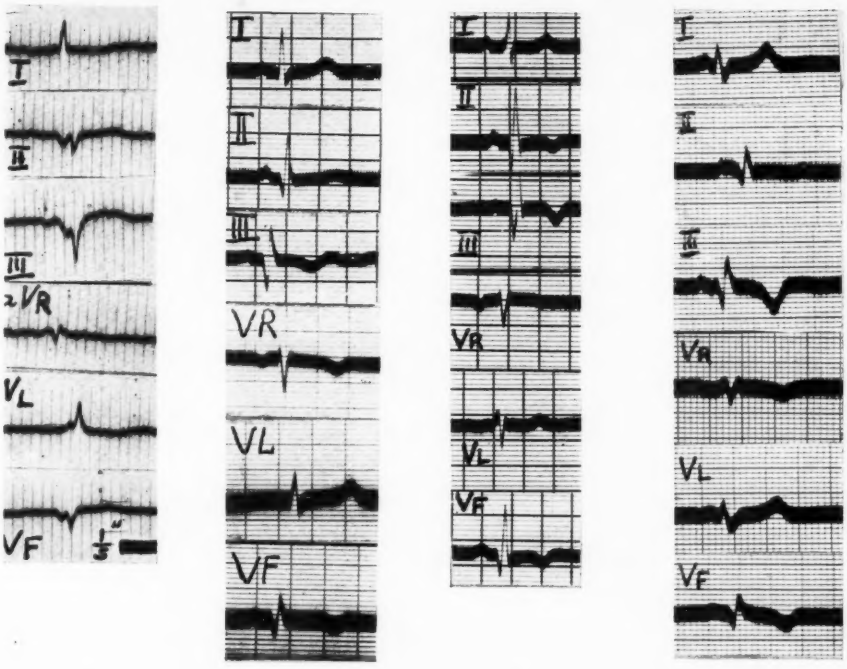


FIG. 4.—Unipolar limb leads in cardiograms with characteristic changes in the standard leads.

(A) Case 17: Man aged 61: infarction three years ago.
(B) Case 18: Woman aged 39: infarction two years ago.
(C) Case 1: Man aged 45: infarction three weeks ago (10 days after the tracing shown in Fig. 1A).
(D) Case 19: Man aged 54: infarction nine weeks ago.

upright in the left leg, or downward in the left arm, or if an initial R shown in the right arm was also recorded in lead I as a Q of similar size; a Q in the left leg did not represent infarction if it was of the same amplitude as Q III. When the standard leads were concordant, equivocal Q waves in lead II and III were suggestive of infarction if Q in the left leg lead was smaller than Q III and the right and left arm leads conformed to the infarction pattern. In discordant tracings, care had to be taken to ascertain that the downward deflection in lead III was a Q and not an S wave. A true Q III stood for infarction if Q in the left leg lead was 0·04 second or more in width; a deep Q, even when smaller than Q III, did not indicate an infarct in this type of tracing. If Q III was abolished by deep inspiration, absence of Q in lead VF could be inferred and infarction was unlikely; the effect of deep inspiration was inconclusive if it left Q III unchanged or reduced in size.

## DISCUSSION

The preceding observations have shown the unipolar limb leads to be of value in the cardiographic diagnosis of posterior infarction. In the past, the unipolar left leg lead was singled out for examination in cases of posterior infarction, and the diagnostic significance of deep and wide Q deflections in this lead was stressed (Myers and Oren, 1945; Goldberger, 1947). Although such Q deflections were found in the present series of cases, difficulties arose because there were patients with infarction who exhibited a small and short Q, and subjects without infarction with deep Q waves in lead VF. When such equivocal cardiograms were studied, examination of the other unipolar limb leads was valuable.

On theoretical grounds, changes in the curves of the left and right arm must be expected with the development of a Q in the left leg lead due to

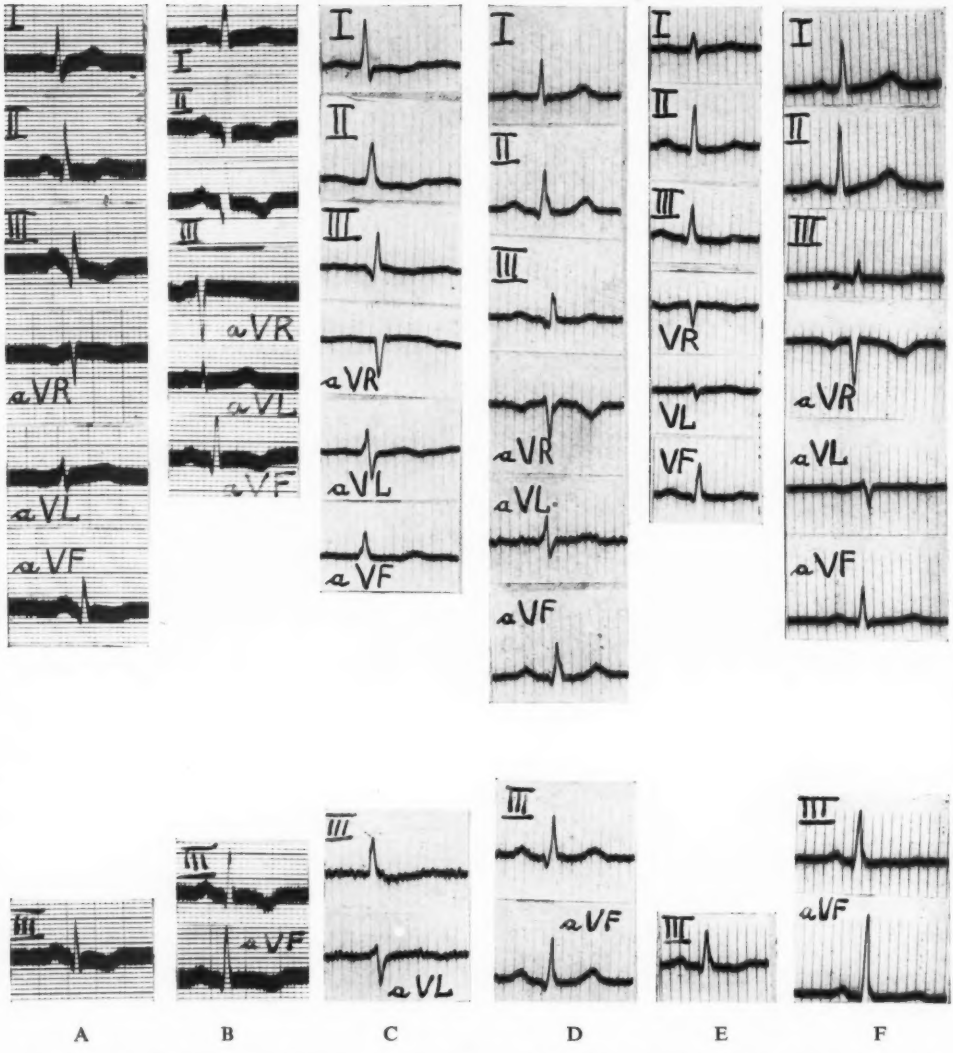


FIG. 5.—Unipolar leads in cardiograms with equivocal Q deflections in the standard leads (concordant type).

Lower row: Leads taken on deep inspiration.

(A) Case 20: Man aged 49: infarction nine months ago.
(B) Case 21: Man aged 38: repetitive paroxysmal tachycardia.
(C) Case 22: Woman aged 36: mitral stenosis, aortic incompetence, auricular fibrillation.
(D) Case 23: Man aged 53: infarction one year ago.
(E) Case 24: Man aged 64: emphysema and bronchitis.
(F) Case 25: Woman aged 47: hypertension

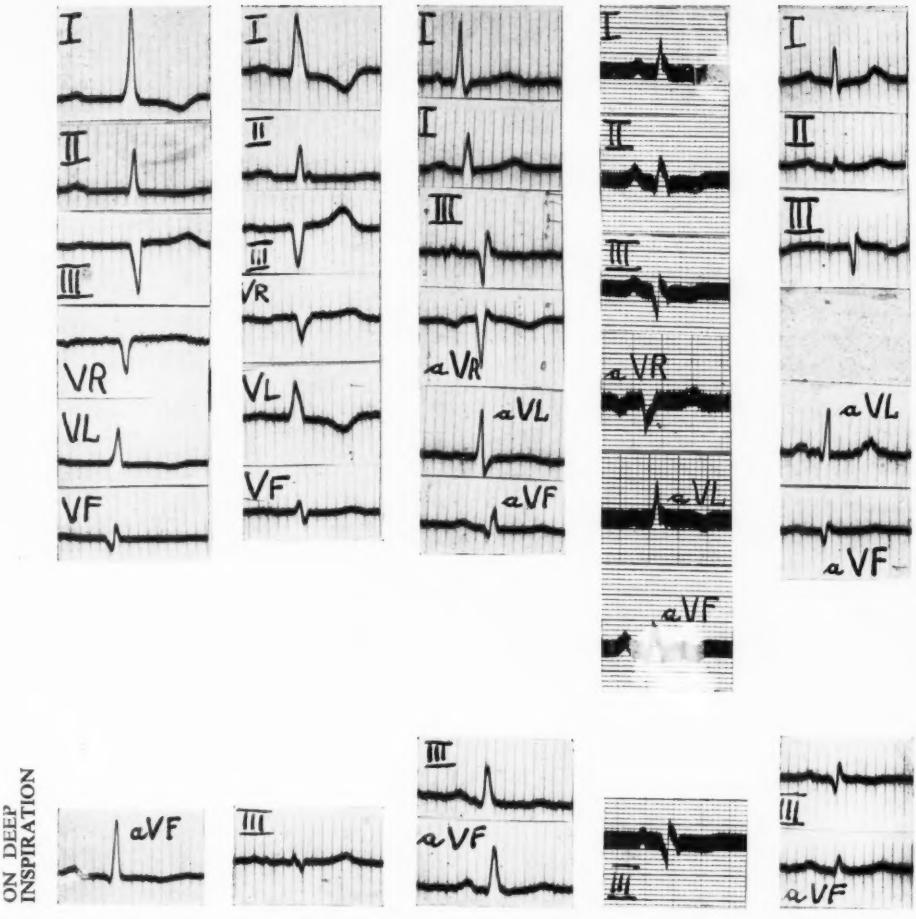


FIG. 6.—Unipolar leads in cardiograms with equivocal Q deflections in the standard leads (discordant type).

Lower row: Leads taken on deep inspiration.

(A) Case 9: Man aged 57: hypertension and posterior infarction (see also Fig. 2A, 3A and B).
(B) Case 26: Man aged 63: hypertension.
(C) Case 27: Man aged 57: hypertension.
(D) Case 28: Man aged 49: infarction four weeks ago.
(E) Case 29: Woman aged 69: moderate hypertension.

infarction as the sum of the potentials in the three limbs leads must remain zero at any given time. Examination of the standard leads had shown that a Q I present before infarction is reduced in size or abolished by the infarct; since such Q waves usually derive from an initial negative deflection in the left arm lead, it was expected that the development of early negativity in the left leg lead from infarction would cause early positivity in the left arm lead, and this has been confirmed by observation. As the upward deflection in the left arm lead is a counterpart of Q in the left leg lead, it follows that it must occur early in ventricular excitation and be synchronous with Q in the left leg lead. Lead I

measures the potential difference from the left to the right arm; a Q in the left arm or an R in the right arm will be recorded as a Q in lead I. Since early negativity in the left arm does not occur in these cases of posterior infarction, a Q in lead I can only be due to early positivity in the right arm; but the positive deflection in the left arm must partly or wholly counteract the formation of a Q in lead I from the positive deflection in the right arm; therefore, Q I is smaller than R in V R, or it is absent. Observation has confirmed this argument. In the absence of infarction, a Q in the left leg lead is not necessarily combined with a prominent R in the left arm lead: the initial deflection may be of low voltage (Fig. 5E and F) or may be directed downward (Fig. 6E). There is also the possibility that R in the left arm lead may not occur early in ventricular excitation: this can be recognized if the R wave does not interfere with the formation of a Q I from R in the right arm lead. Such a combination of events has been seen in one record (Fig. 5B).

When the standard leads are concordant, infarction is likely if Q III is larger than Q in the left leg lead. This is an indirect method of observing the early upright deflection in the left arm which reinforces the downward direction of Q III initiated by Q in the left leg; in the absence of infarction, the small amplitude of R in the left arm prevents this reinforcement of Q III. Discordant cardiograms usually show a prominent R in the left arm lead; hence Q III is larger than Q in VF also in the absence of infarction. Deep inspiration, by causing a shift of the long axis of the heart away from the left arm, reduces the amplitude of R in VL (Fig. 5C); it therefore abolishes the Q waves which are not due to a Q in the left leg lead.

In the left leg lead, a Q of infarction may be small in size and duration in concordant tracings. It is wide though not necessarily deep in cardiograms of the discordant type, when a wide and deep Q III is also shown; but a wide and deep Q in lead III alone does not stand for infarction because it also occurs from left ventricular hypertrophy (Myers and Oren (1945); also Fig. 6B).

## Summary and Conclusion

The electrocardiograms of 40 patients with posterior infarction were examined for modifications of the QRS complex indicating infarction; there were 7 cases with inconclusive Q waves in lead III, or II and III, and they closely resembled cardiograms from subjects without infarction. In concordant tracings, uncertainty was caused by small Q waves in leads II and III; in the discordant type, difficulties arose when Q was deep, or wide and deep, in lead III, and small or absent in lead II; care had to be taken to examine each beat in lead III to ascertain that the downward deflection in this lead was not in fact an S wave. A Q wave in lead I was more often seen in normal subjects than after infarction, but this was of no diagnostic significance; in the individual patient, such a Q wave shown before infarction was reduced in amplitude or abolished by the infarct.

Unipolar limb leads were examined in 18 cases of posterior infarction with Q waves in the standard leads. The left leg lead showed a Q deflection in all cardiograms; it was deep and wide if typical Q waves were seen in leads II and III. When the standard leads were discordant with a wide and deep Q III, Q in the left leg lead was wide, but not always deep. When the standard leads were concordant with inconclusive Q waves in leads II and III, Q was also small in the left leg. In all records of plain posterior infarction, Q III was larger than Q in the left leg; the left arm lead showed an initial upright deflection of more than 1 mm.; in most, but not all records, an initial upright deflection was also shown in the right arm, and this did not appear as a Q wave of the same size in lead I.

From an examination of unipolar limb leads in subjects without infarction it was concluded that equivocal Q waves in the standard leads did not indicate plain posterior infarction if the initial deflection was upright in the left leg, or downward in the left arm, or if an initial R shown in the right arm was also recorded in lead I as a Q of similar size. A Q wave in the left leg lead did not represent infarction if it was of the same amplitude as Q III. When the standard leads were concordant, equivocal Q waves in leads II and III were suggestive of infarction if Q in the left leg lead was smaller than Q III and if right and left arm leads conformed to the infarction pattern. In discordant tracings, the width of the Q wave in the left leg lead was significant; a deep Q wave, even when smaller than Q III, did not indicate an infarct. The effect of deep inspiration on the Q wave in lead III and lead VF was also examined; if Q III was abolished by deep inspiration, absence of Q in lead VF could be inferred.

In the discussion, the electrical events leading to the observed cardiographic patterns were analysed.

I wish to record my gratitude to Dr. William Evans for much advice and encouragement received from him.

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# TRANSPOSITION OF THE AORTA AND PULMONARY ARTERY DEMONSTRATED BY ANGIOCARDIOGRAPHY

BY

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Complete transposition of the great vessels is one of the less common congenital anomalies. Survival after birth is dependent upon the presence of some communication between the right and left sides of the heart that will permit crossing of the greater and lesser circulations and enable venous blood to reach the lungs.

The case described below is of particular interest because of the absence of diagnostic criteria afforded by the usual methods of clinical and radiological examination.

## Case Report

D.T., aged 5 years, had been cyanosed since birth. He became very breathless on the slightest exertion and he frequently assumed the squatting position. There was no history of rubella during the mother's pregnancy.

*Physical examination.* The child was undersized, with marked cyanosis which was of equal intensity in both the upper and lower extremities. There was dyspnœa at rest and marked clubbing of the fingers and toes. Examination of the cardiovascular system showed bulging of the præcordium and slight general cardiac enlargement. A harsh systolic murmur was heard down the left side of the sternum, and there was a pure pulmonary second sound. There was no thrill and no diastolic murmur. The femoral pulses and blood pressure were normal, and the lungs were clear.

The blood count showed a considerable degree of polycythæmia. The figures with the normal values at the age of 5 years for comparison were as follows: hæmoglobin 21 grams (12·6), red blood corpuscles 7·9 million per c.mm. (4·6), leucocytes 12,000 per c.mm., mean corpuscular diameter 7·3$\mu$ (7·4), packed cell volume 63 per cent (37), mean corpuscular volume 80 c.$\mu$ (80), mean corpuscular hæmoglobin concentration 33 per cent (34).

*Cardiography*, using augmented unipolar leads in addition to standard leads, was performed and has been interpreted according to the criteria of Goldberger (1947) (Fig. 1). The standard limb leads show high voltage complexes and marked right axis deviation. The P waves in leads I and II and VF are of increased amplitude and duration (lead I, duration 0·11 sec., height 2 mm.; lead II, duration 0·12 sec., height 3 mm.; lead VF, duration 0·11 sec., height 2·5 mm.). The heart is vertical in position, since the unipolar left leg lead resembles lead V6 and therefore faces the epicardial surface of the left ventricle. There is also clockwise rotation of the heart round its long axis, because the unipolar left arm lead faces the cavity of the right ventricle. VL shows a small R wave and a large S wave and a negative T wave and the præcordial leads show RS patterns.

There is no definite evidence of right ventricular strain, but this may be deduced from the presence of auricular hypertrophy. Goldberger states that if any of the unipolar extremity leads show P waves with duration of 0·11 sec. or more and an amplitude of 2·5 mm. or more, auricular hypertrophy may be suspected.

*Radiography.* A postero-anterior radiogram of the chest showed an enlarged heart with a prominent pulmonary conus and full root shadows; the lung fields showed congestive changes (Fig. 3).

Fluoroscopy and barium swallow revealed an enlarged heart, with an enlarged pulmonary conus, and very dilated pulmonary vessels with marked pulsation. The aorta appeared to be dextroposed.

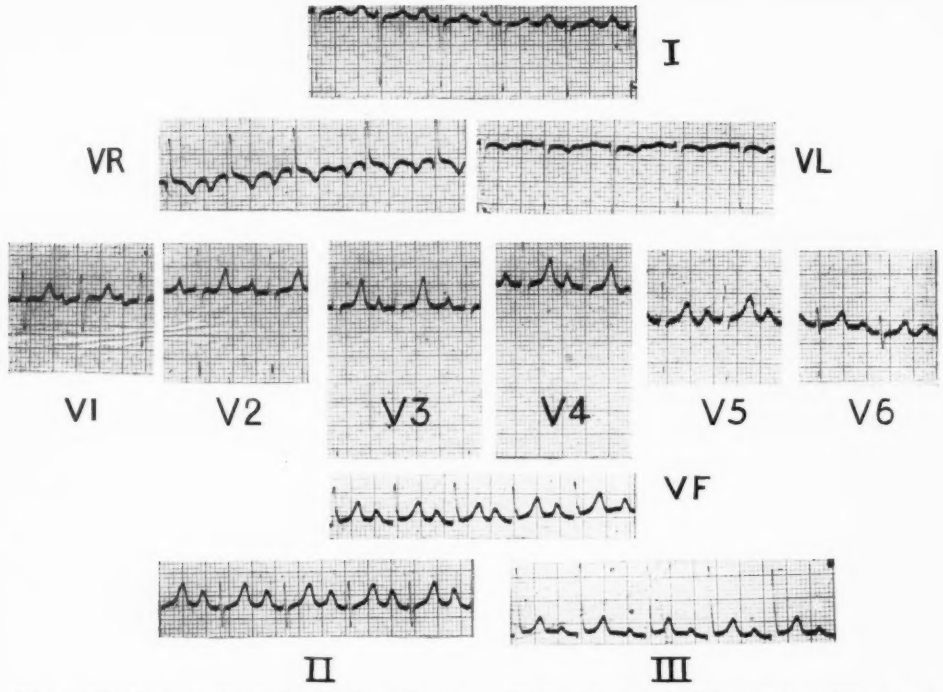



FIG. 1.—Standard and unipolar lead electrocardiograms. The heart is vertical with clockwise rotation round its long axis. Right auricular strain and indirect evidence of right ventricular strain are present.
Limb lead 1 mv.=1 cm. Præcordial leads 1 mv.=1·5 cm.

### ANGIOCARDIOGRAPHY

*Technique.* Angiocardiography was carried out under general anæsthesia. Two injections of 40 ml. 70 per cent pyelosil were made into the antecubital vein of the right arm. In the first instance the patient was X-rayed in the right posterior oblique position lying supine, and in the second instance in the antero-posterior position lying on his side.

A rotating serial cassette changer was used with the following radiographic factors: 200 M.A. 72–74 K.V.P., 1/20th second exposure, at a target film distance of 36 inches. In both antero-posterior and oblique positions six exposures were made at one-second intervals starting at one second after the injection.

*Oblique radiograms. On the two-second film* (Fig. 3) good filling of the superior vena cava will be noted. The right auricle is clearly outlined and the reflux of contrast medium into the inferior vena cava is seen. The right ventricle is filled and enlarged and the interventricular septum is convex posteriorly. The ascending aorta and arch are outlined and a faint trace of contrast medium is visible in the left side of the heart just posterior to the right auricle. The pulmonary artery is outlined very faintly.

*On the three-second film* (Fig. 4) the right auricle is still outlined and the ventricle is more clearly shown, as well as the ascending aorta, aortic arch, and descending aorta. The innominate, and external and internal carotid arteries are also outlined. The left auricle and ventricle are fairly well delineated and the pulmonary artery can now be seen clearly demonstrated as a second arch below the aorta. *On the subsequent films* most of the contrast medium is seen scattered throughout the pulmonary vascular bed and the cardiac chambers are not clearly differentiated.

*Antero-posterior radiograms. In the two-second film* (Fig. 5A and B) the right auricle and ventricle are clearly demonstrated. The ascending aorta is seen to arise from the right ventricle. The

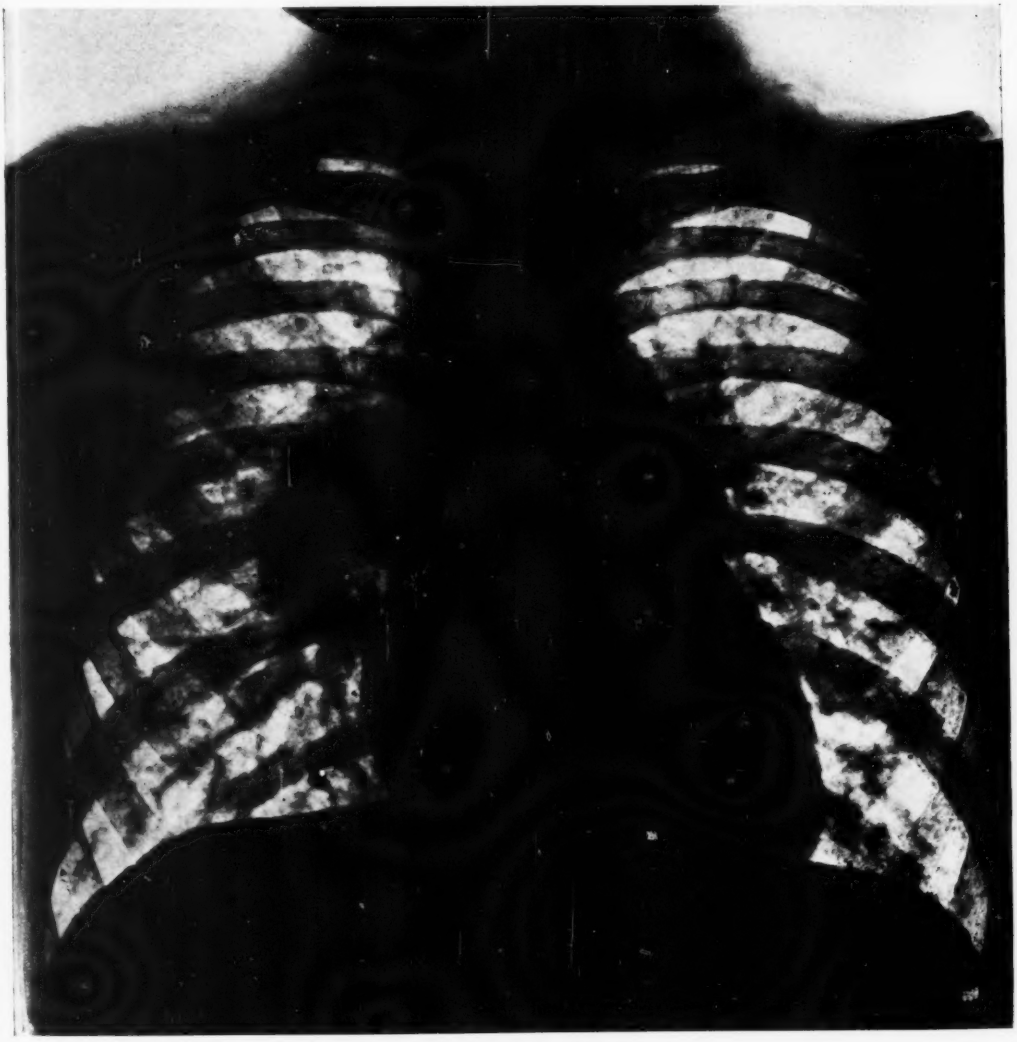
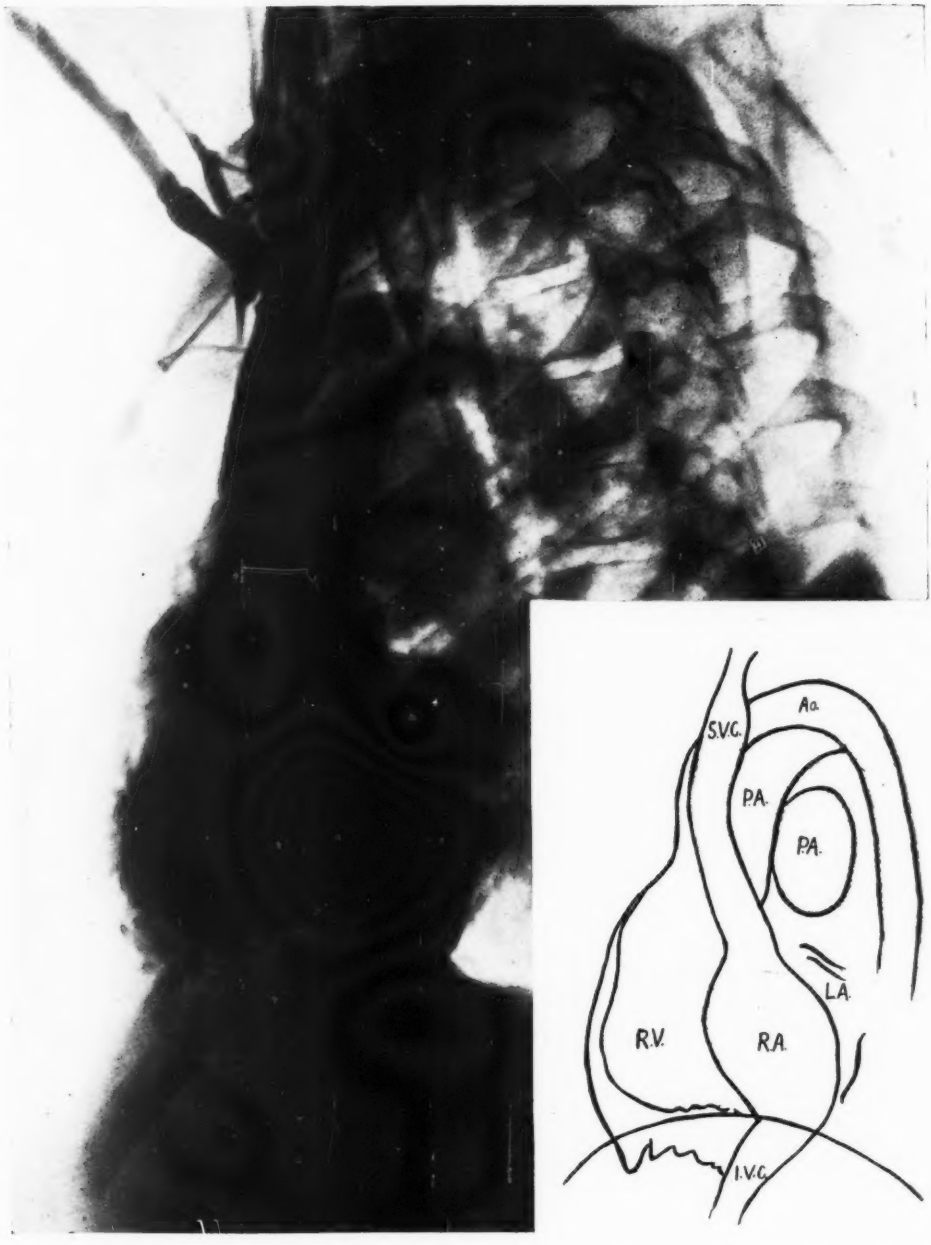


FIG. 2.—Postero-anterior 6-ft. film of the chest.

innominate artery, the right carotid and the internal carotid arteries are shown and some contrast medium has entered the left ventricle. *On the three-second film* (Fig. 6) the left side of the heart is now filled with contrast medium. The aorta is still shown; the pulmonary artery and the main pulmonary branches are partly demonstrated. As in the case of the oblique radiograms subsequent films did not reveal any details of the cardiac chambers as most of the contrast medium had entered the pulmonary vascular bed and partly left the heart.

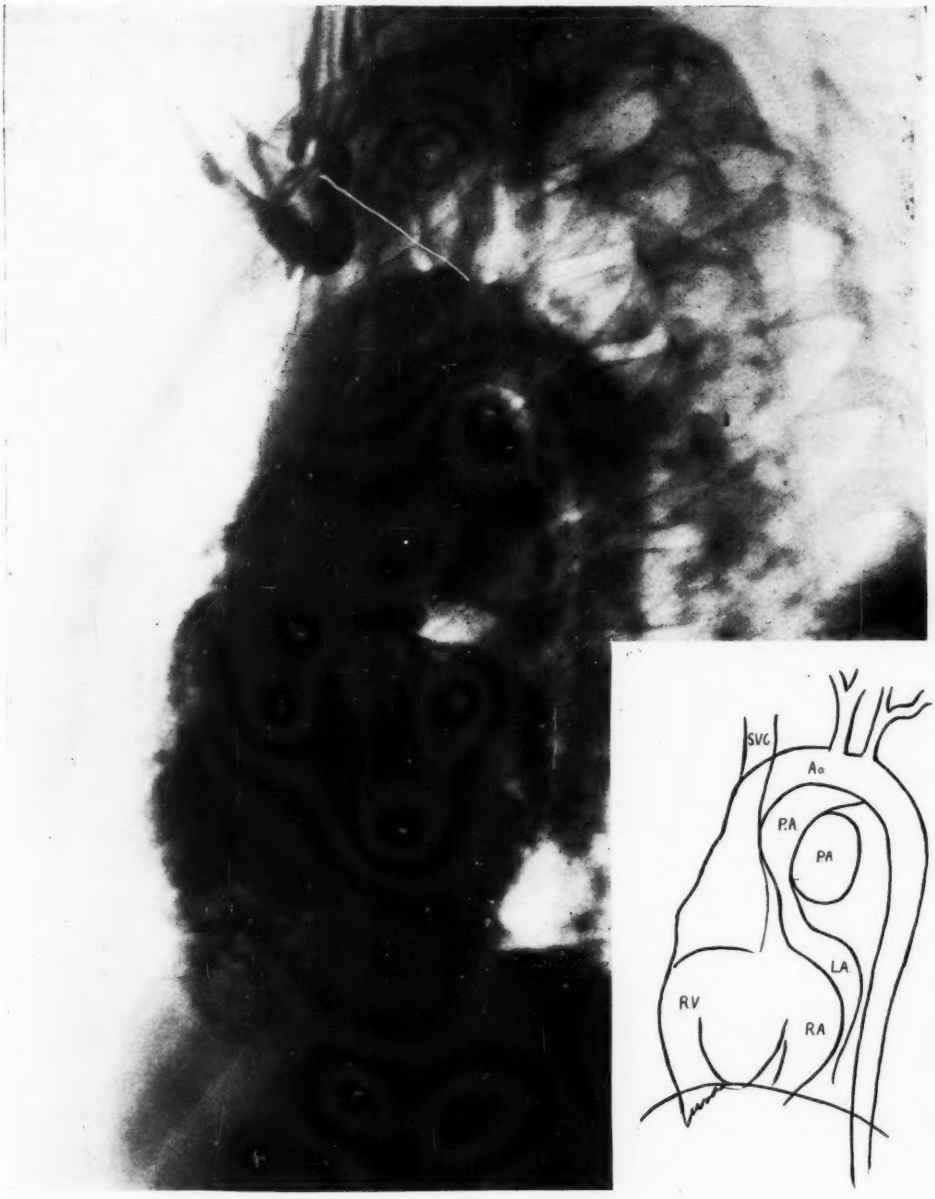
The radiographic examination quite clearly demonstrated the transposition of the aorta and pulmonary artery. The septal defect itself is not shown, but the rapid filling of the left side of the heart on the two- and three-second films is very suggestive of the presence of such a defect. It is




A B

FIG. 3.—Angiocardiogram at 2 seconds. Patient in the right posterior oblique position. The right auricle and ventricle are demonstrated as well as the pulmonary artery and aorta.

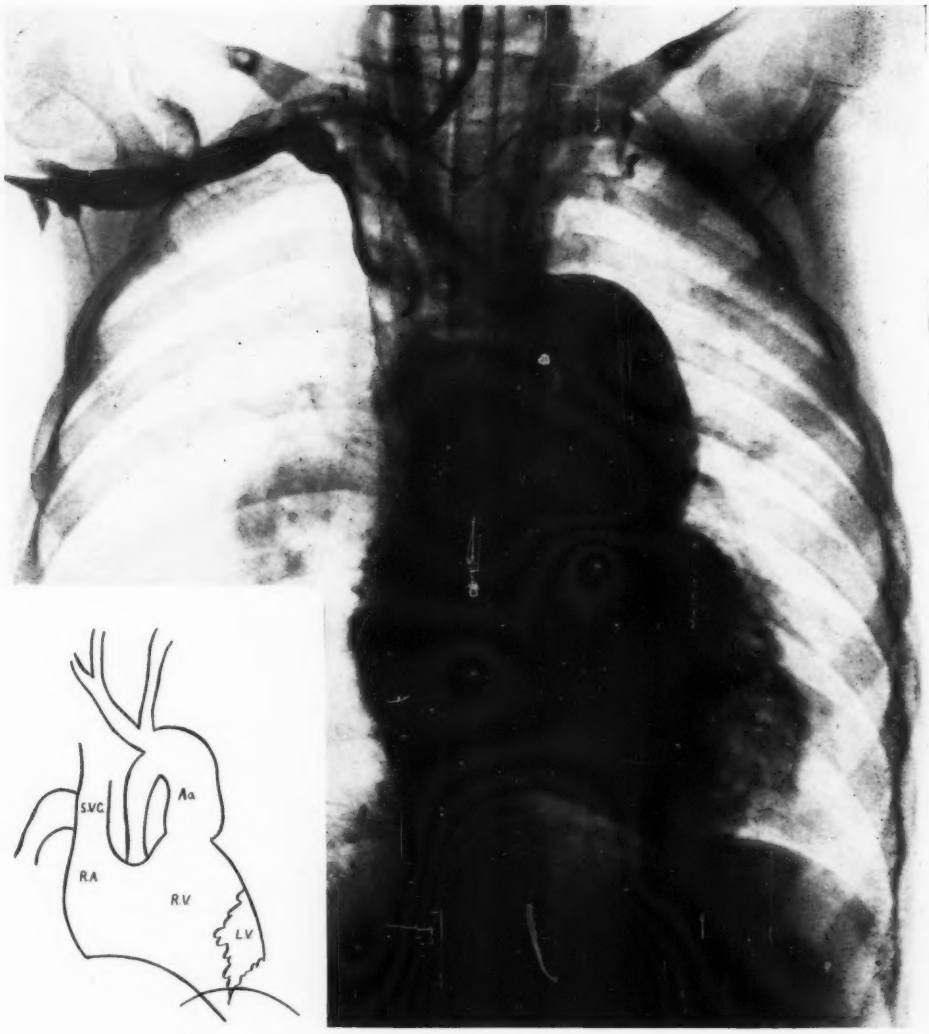
(B) (Inset) Diagram of Fig. 4A. S.V.C. = Superior vena cava; I.V.C. = Inferior vena cava; R.A. = Right auricle; R.V. = Right ventricle; L.A. = Left auricle; P.A. = Pulmonary artery; Ao. = Aorta




A B

FIG. 4.—Angiocardiogram of the patient in the oblique position taken at 3 seconds. Pulmonary artery and aorta are clearly demonstrated.

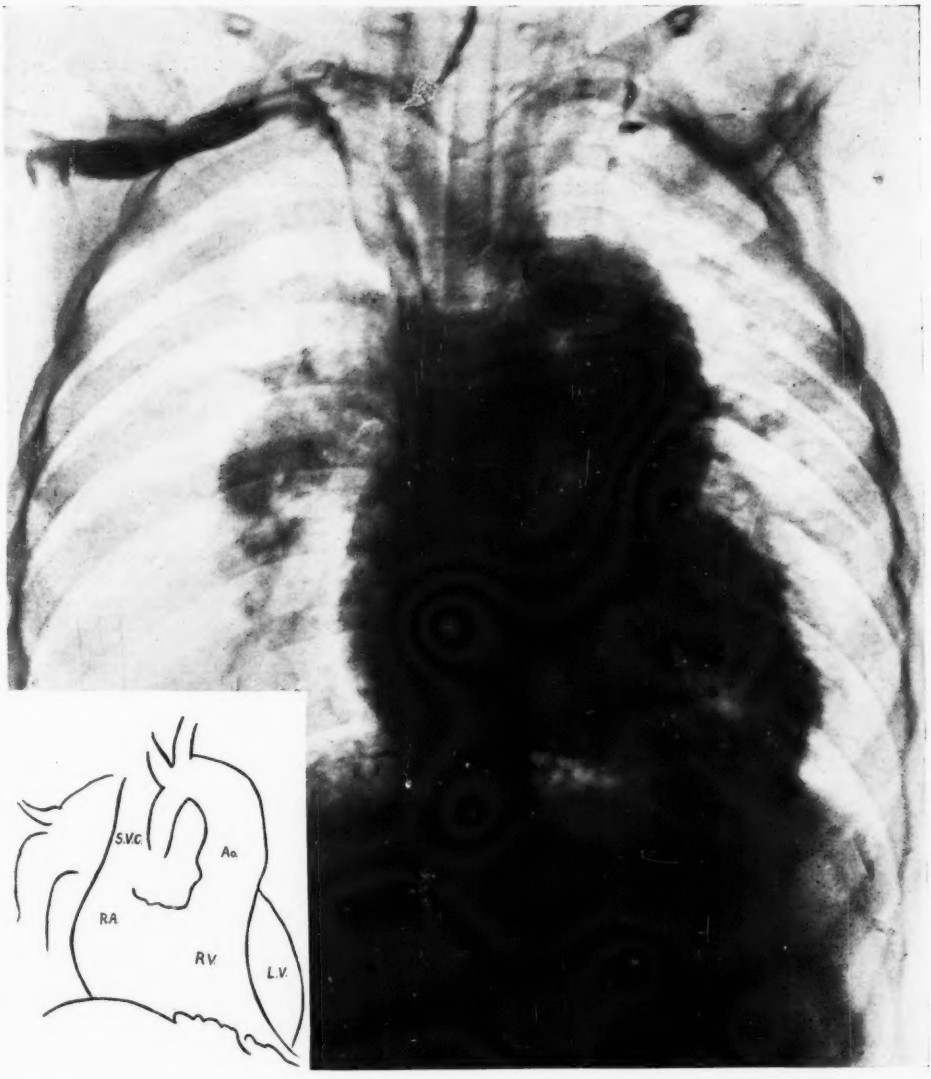
(B) (Inset). S.V.C. = Superior vena cava
R.A. = Right auricle
R.V. = Right ventricle
P.A. = Pulmonary artery
L.A. = Left auricle
Ao. = Aorta




B A

FIG. 5.—Angiocardiogram, at 2 seconds, of the patient in the antero-posterior position. Right auricle and ventricle are clearly demonstrated. The aorta is seen to rise from the right ventricle.

(B) (Inset). S.V.C. = Superior vena cava
R.A. = Right auricle
R.V. = Right ventricle
L.V. = Left ventricle
Ao. = Aorta




B A

FIG. 6.—Angiocardiogram, at 3 seconds, of the patient in the antero-posterior position. The right ventricle, aorta and the left ventricle are outlined.

(B) (Inset). S.V.C. = Superior vena cava
R.A. = Right auricle
R.V. = Right ventricle
L.V. = Left ventricle
Ao. = Aorta

impossible to decide if this defect is auricular or ventricular.

Cardiac catheterization was not undertaken as it was felt that it would yield no further useful information.

## Differential Diagnosis

The history of cyanosis from birth and the physical signs in this case suggested either transposition of the aorta and pulmonary artery with an associated widely patent septum, tricuspid atresia, single ventricle, or Fallot's tetrad with extreme pulmonary stenosis. Electrocardiography did not reveal the gross right or left heart strain that would have been expected in pulmonary and tricuspid atresia respectively. Taussig (1945) describes a characteristic cardiac contour on fluoroscopic examination in cases of transposition of the great vessels. Since the aorta lies further to the right and in front and the pulmonary artery further to the left and behind, the shadow at the base of the heart is the reverse of normal, being wider in the left anterior oblique view and narrower in the antero-posterior view. In the latter position the shadow of the pulmonary conus is usually absent and a rhythmical change in size of the right auricle and ventricle, due to frequent reversal of the shunt, is seen. In our case no such distinctive contour or rhythmical alteration was observed, and a pulsating shadow noted in the region of the pulmonary conus was proved by angiocardiography to be the aorta.

## Discussion

Complete transposition of the aorta and pulmonary artery may be accompanied by patencies of the normal fœtal pathways, the foramen ovale, and the ductus arteriosus, or by additional septal defects. As Taussig (1947) points out, the larger the communication between the two sides of the heart, the longer will be the period of survival. When the ductus arteriosus or foramen ovale alone are patent, survival for more than a few hours or days does not occur, but infants who in addition have widely patent interventricular septa may survive for much longer. Taussig considers that even in cases where both septa are widely patent survival is rarely possible beyond the age of eighteen months. Hanlon and Blalock (1948) collected 123 cases of complete transposition with associated abnormalities and found the average duration of life was nineteen months. Six patients lived ten years or longer, but the average age at death in the other 117 patients was five and a half months. Twelve cases had an interventricular septal defect without other abnormalities, and these patients lived for a mean period of four years and one month. The association of a patent foramen ovale with patent interventricular septum (19 cases) increased the survival to four years nine months, but the association of other defects decreased the duration of life. Of Kato's (1930) 86 cases, 16 had defects of both septa, the average survival time of these 16 being five and a half years. But the inclusion of 2 patients aged nineteen and fifty-six years respectively among these 16 cases presents a falsely optimistic picture. It appears, therefore, that complete transposition is unlikely to be compatible with survival after the age of four years, even when a patent interventricular septum is present.

## Summary

A case of complete transposition of the aorta and pulmonary artery is described in a child five years of age showing intense cyanosis and great breathlessness on exertion. The condition was clearly revealed by angiocardiography and could not have been detected by the usual clinical and radiological methods. A survey of the literature shows that survival beyond the age of four and a half years is very rare in this condition.

We wish to thank Professor R. S. Illingworth for permission to publish the details of this case, Dr. J. Wilkie and Dr. C. W. Lawson for their help and co-operation, and Mr. J. Coombs for technical assistance.

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# THE RESULTS OF MEDICAL AND SURGICAL TREATMENT OF ESSENTIAL HYPERTENSION

BY

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For a variety of reasons it is difficult to evaluate the influence of therapeutic procedures in essential hypertension, the peculiar feature of which is an elevation of the diastolic blood pressure. Patients present individual problems and do not readily adapt themselves to precise categories and strict comparisons. Furthermore, while hypertension commonly runs a prolonged course over the years and shows of itself spontaneous fluctuations from day to day, yet for reasons unknown the intensity of the disease may abruptly increase and the pace towards a fatal termination quicken with unexpected suddenness. We have no measure of vascular vulnerability with which to compare one patient with another.

A feature of the disease, even in the same subject, is its variability. Symptoms pass through phases of activity and seldom correlate with the blood pressure readings. Arteriolar tone is not a fixed quantity. The diastolic pressure is constantly changing, occasionally falling to surprisingly low levels for no obvious reasons. It is remarkable how, after many months of intermittent disablement by headache or giddiness in middle life, a symptom-free stage may ultimately be attained in later years without, however, much significant alteration in the blood pressure. These natural variations and remissions hinder reliable therapeutic deductions in the individual patient. Nervous and emotional factors are difficult to assess and it is well recognized that the hypertensive patient is highly susceptible to suggestion—particularly when it is reinforced by the sympathetic care and understanding of an enthusiastic adviser. Psychological factors may distort the picture and obscure the basic facts.

By the study of a group of patients over a sufficiently long period the fallacies attributable to the inconsequential fluctuations of pressure and spontaneous remissions in symptoms are minimized to some extent. All our patients were under the care and supervision of the same observers: accustomed to the same surroundings, the same methods of clinical investigation and familiar with the ways of the examiners, they were thereby exposed to few extraneous factors liable to influence their nervous tension adversely. By the adoption of an attitude of benevolent neutrality, psychological influences were kept as uniform as possible from patient to patient. Each patient reported at intervals and was assessed by the same observers.

Many attempts have been made to judge the efficacy of the surgical attack on hypertension (Adson *et al.*, 1934, 1936; Allen and Adson, 1940; Smithwick, 1940, 1944; and Grimson, 1947). Inadequate standards for comparison have proved a stumbling-block. Not infrequently an author has assembled two groups for comparison, one medically and the other surgically treated. To some extent the conclusions are invalidated by a comparison of the author's series of surgically treated patients with a medical group investigated by someone else necessarily employing slightly different standards, techniques, and methods. For example, Wagener and Keith (1939) report on a series of medically treated patients with hypertension and their results have been used by several surgical authors for comparison with their own cases; Flaxman (1944) describes a medical series of his own compared with the surgical experiences of Peet *et al.* (1940); Hammarström (1947) compares his surgical cases with a series of non-operated cases described by Bechgaard (1946), and so on. The general consensus of opinion is that sympathectomy is of value particularly in younger patients before the development of serious coronary or renal disease.

* Working under the tenure of a Scholarship awarded by the Grocers' Company of London.

Hammarström (1949) believes that in the severer cases with retinal exudation life expectancy is increased in a sympathectomized group as compared with similar patients treated by medical means.

## The Problem

The problem under consideration is the evaluation of the results obtained by medical and surgical means in the treatment of essential diastolic hypertension. This has involved a review of the progress of a large number of patients of whom some were surgically and some medically treated. The results are considered in general as well as in certain particular details. In the investigations now to be described, both " medical " and " surgical " groups have been examined and assessed by the same doctors, thus ensuring, it is hoped, more constant standards of comparison and hence more accurate conclusions. Surgery was first employed by us nine years ago. All the cases subsequently sympathectomized have been followed-up and form the basis of the present study. The control medical group dates back to five years ago.

## The Material

The material on which our investigations are based consists of 151 cases of essential hypertension of whom 96 were treated by medical measures and 55 by surgery.

The investigations common to all the patients started on their admission to hospital. In general arteriosclerosis, angina, congestive heart failure, poor renal function, and an age in excess of 50 years, with few exceptions, were usually regarded as contra-indications to surgical intervention, but minor cerebral episodes, even transient hemiplegias, did not exclude the possibility of surgical help. Changing standards of selection for surgery have proved of help to us in the construction of the two groups —surgical and medical—for the purposes of the present analysis of the results obtained.

When surgery was not employed the medical measures recommended were those in common use, including in the first instance a rest in bed in the hospital for two or three weeks, and thereafter some limitations in activities, a reduction in body-weight when necessary, the administration of simple sedatives such as phenobarbitone and analgesics from time to time, the use of the " head-up " bed for the prevention of morning headache, and venesection very occasionally. Most emphasis was put on reduced activities and the avoidance of fatigue. In the surgical group Smithwick's (1940) method of lumbo-dorsal sympathectomy was employed in 75 per cent of the 55 patients and lumbar sympathectomy in the remainder treated several years earlier.

The medically treated group of 96 cases consisted of 76 benign (that is with retinal changes less than papillœdema) and 20 malignant cases (that is with papillœdema accompanied or unaccompanied by other retinal changes); the surgically treated group of 55 was composed of 45 benign and 10 malignant cases.

The " benign medical " group consisted of 76 cases, 17 males and 59 females, varying in age from 30 to 71, the average age being 47 years; the duration of the follow-up period varied from six months to five years. The " benign surgical " group was composed of 45 cases, 18 males and 27 females, varying in age from 19 to 60, the average age being 40 years; the follow-up periods varied from three months to eight and a half years.

The " malignant medical " group contained 20 cases, 14 males and 6 females, varying in age from 31 to 66, the average age being 50 years; the follow-up periods ranged from one month to one year. The " malignant surgical " group was composed of 10 cases, 5 males and 5 females, whose ages ranged from 36 to 61, the average age being 46 years. Follow-up periods varied from three months to three years.

## Method of Investigation

*Assessment of patients before and after treatment.* The same routine of tests and investigations was applied to every patient in the series before treatment and at intervals after treatment. The methods employed consisted of a careful history to exclude any primary renal disease, endocrine disorder, or other cause for the hypertension. Particular attention was devoted to a routine physical examination with special note of the following points.

(1) Assessment of retinal grade according to the method of Wagener and Keith (1939) into four classes—1, 2, 3, and 4. (Normal is graded 0, papillœdema is graded 4.)

(2) Assessment of cardiac efficiency, graded according to the following method: A, normal; B, slight impairment during exertion; C, considerable impairment during exertion; and D, impairment at rest.

(3) Assessment of renal efficiency, according to results of the urea concentration range (Cameron, 1934) or the urea clearance tests (Peters and Van Slyke, 1946) thus: A, very good; B, good; C, fair; and D, poor.

(4) Assessment of severity of symptoms, thus: A, symptom-free; B, moderate symptoms but fit for work; C, severe symptoms, unfit for work; and D, dead.

(5) Assessment of the diastolic pressure. As a measure of the peripheral resistance the diastolic

pressure is recognized as a more reliable indication of the severity of the hypertensive process than the systolic level. Furthermore, the diastolic pressure has a smaller range of fluctuation than the systolic and is less susceptible to unpredictable excursions. For comparative purposes the diastolic pressure therefore yields the more reliable figure and we have made use of it in our assessment. The basic figures were taken when the patient, already thoroughly familiar with the method, had rested for at least 10 to 15 minutes recumbent on a couch. It must be realized that this reading was not taken until the end of the examination, by which time it was ensured that the patient was adjusted to his surroundings and completely at ease in a quiet restful room with which he was familiar. The diastolic pressure is recorded in mm. of mercury for each patient and not graded A, B, C, or D as for the other observations listed above.

During the clinical examination note was made of the physique and nutrition of the patient, the pattern of the electrocardiogram, and the heart-size measured radiologically by the method of Ungerleider and Gubner (1942). These latter observations, however, had not all been made in every case before treatment, and therefore were discarded in the statistical analysis of the results.

*The construction of matched groups for comparison of results.* The second part of the investigation consisted in dividing the patients into matched groups for the purpose of comparing the results of the two methods of treatment. As the hypertensive process as a rule runs a milder course in the female (Bechgaard, 1946; Rogers and Palmer, 1946–7) the surgical cases were divided on a sex basis. Each of these male and female groups was subdivided into smaller groups composed as far as possible of persons of similar ages and with similar grading in the tests listed above. This procedure resulted in the "surgical" cases being divided into 11 female and 8 male groups, as shown in Table I.

Next, each "medical" patient's results were carefully scrutinized, and he was placed in a "medical" group corresponding to the "surgical" group whose criteria he best fitted. Those medical cases who fitted exactly were termed "first-class comparisons"; those who fitted well, but deviated in one degree in any criterion other than retinal grade were termed "second-class comparisons"; those who fitted less well, but better into that group than into any other were called "third-class comparisons" and were excluded from the statistical assessment of results.

There now existed 8 male and 11 female groups each consisting of the original surgical cases and those medical cases that matched them, the matching being done on the basis of their pre-treatment investigations. The addition of the medical cases as an "extension" to each surgical group caused no alteration in the description of any group as given in the above tables, since the third-class comparisons (which might have disturbed the homogeneity of a group) had been discarded. The final constitution of each "surgical-plus-medical" group which are the units on which the actual work of comparison and statistical analysis was done is presented in Table II. Amongst the males groups 1 to 4, inclusive and amongst the females groups 1A to 4, represent cases of benign hypertension. Malignant hypertension is composed of groups 5B and 5C male, and groups 5A and 5B female.

TABLE I

COMPOSITION OF GROUPS OF SURGICALLY TREATED PATIENTS

| Group | Retinal grade | Cardiac efficiency grade | Renal efficiency grade |
|---|---|---|---|
| | | *Males* | |
| 1 | 0 | A | A |
| 2 | I | A | A |
| 3 A | II | A | A–B |
| 3 B | II | B | A–B |
| 4 | III | C | C |
| 5 A | IV | A | B |
| 5 B | IV | C | C |
| 5 C | IV | D | D |
| | | *Females* | |
| 1 A | 0 | A | A |
| 1 B | 0 | A | B |
| 1 C | 0 | B | A |
| 2 A | I | A | A |
| 2 B | I | A | B |
| 2 C | I | C | C |
| 3 A | II | A | A |
| 3 B | II | C | A |
| 4 | III | A–B | C |
| 5 A | IV | B | B |
| 5 B | IV | C | C |

Of the total of 23 male surgical cases, 18 were benign and 5 malignant; and of the total of 27 medical cases used for the analysis (1st+2nd class) 13 were benign and 14 malignant. Of the total of 32 female surgical cases, 27 were benign and 5 malignant; of the total of 47 female medical cases (1st class+2nd class comparisons) 42 were benign and 5 were malignant (Table II).

The third class comparisons numbered in all 22, 4 males and 18 females. Of the 4 males, all were benign cases; of the 18 females, 17 were benign, and 1 malignant.

It is customary to consider the adverse influence of obesity on the course of hypertension. It has

TABLE II

COMPOSITION OF THE MATCHED GROUPS ON WHICH THE STATISTICAL ANALYSIS IS BASED. THE THIRD CLASS COMPARISONS ARE DISCARDED.

| Group | No. of surgical cases | No. of medical cases for comparison | | |
|---|---|---|---|---|
| | | 1st class | 2nd class | 3rd class |
| | | *Males* | | |
| 1 | 3 | 3 | — | — |
| 2 | 5 | 1 | 2 | — |
| 3 A | 6 | 1 | 1 | — |
| 3 B | 2 | 2 | 1 | 3 |
| 4 | 2 | 2 | — | 1 |
| 5 A | 3 | 4 | 3 | — |
| 5 B | 1 | 2 | — | — |
| 5 C | 1 | 1 | 4 | — |
| Total | 23 | 16 | 11 | 4 |
| | | *Females* | | |
| 1 A | 3 | 4 | — | — |
| 1 B | 1 | 3 | 3 | 4 |
| 1 C | 3 | 1 | 4 | 2 |
| 2 A | 2 | 2 | — | — |
| 2 B | 4 | 2 | 2 | — |
| 2 C | 7 | 3 | 2 | 2 |
| 3 A | 3 | 3 | 2 | — |
| 3 B | 3 | 3 | 4 | 6 |
| 4 | 1 | 2 | 2 | 3 |
| 5 A | 4 | 3 | — | — |
| 5 B | 1 | 2 | — | 1 |
| Total | 32 | 28 | 19 | 18 |

been noted by many writers (e.g. Hunter and Rogers, 1923) that since an excess of body weight has an adverse bearing on the subject's expectation of life, it ought to operate even more severely to shorten the life span of the patient with hypertension. Bechgaard (1946), however, notes that contrary to expectation in his series of 1000 hypertensives which contained 311 obese patients, the latter had if anything a lower mortality than the others.

In our small series there were 7 cases of obesity amongst the male surgical patients (5 benign and 2 malignant) and 4 amongst the male medically treated cases (3 benign and 1 malignant). In the females, of those surgically treated, 6 benign and 2 malignant were obese, whilst of the medical series, 19 were markedly overweight. Obesity however had no relation to the mortality rate. Of the 7 " medical " deaths in the benign group only one was an obese individual; the remainder were under average weight. Of the 5 patients who died in the surgically treated group, 3 were under-weight and one average. Obesity did not correlate with any significant deterioration in the course of the follow-up. In fact in the most severe (malignant) hypertensive cases, loss of weight was noted in 65 per cent of the medical and 30 per cent of the surgical cases, and in the medical group it was an accompaniment of their rapid deterioration. Body weight is therefore disregarded in our groupings.

The adoption of matched groups is one which should meet Smithwick's (1948) requirements when he states: " Further comparison of surgically and non-surgically treated cases divided into similar sub-groups in which the most important variables are held constant is desirable. Until this can be done the influence and relative merits of various therapeutic measures upon the course of hypertensive vascular disease cannot be evaluated with certainty." Although the numbers in this investigation are small, our statistical colleague (B.W.) is satisfied that they are sufficiently large to provide information that is significant.

## STATISTICAL ANALYSIS

It must be emphasized strongly that the reliability of this analysis depends entirely on the validity of the grouping and matching of the cases described above. In a clinical trial it is necessary that the allocation of cases to experimental and control groups shall be free from bias in respect of severity of symptoms, age, sex, or any other circumstance likely to have a bearing on prognosis. This is usually contrived by a deliberately planned experiment in which the cases are allotted to one or other form of treatment by a designed process. In the present investigation, however, this was not done; each patient was given surgical or medical treatment as seemed appropriate without strict regard to the possible future use of the cases in a statistical comparison.

It has been possible, however, owing to such factors as changing standards as to indications for operation, patients declining operation, and so on, to match our surgical groups with medical, on the basis of the observations made during the patient's first stay in hospital and thus the series of cases has been converted retrospectively into a properly controlled experiment to the best of our ability. All the patients had been under detailed observation in the wards of the hospital and had submitted to the same routine.

In the statistical analysis each group was taken separately and the " surgical " cases compared with the 1st and 2nd class " medical " cases therein. Six criteria are available for statistical evaluation; these can be divided into two sections. In the first the observations made at periodic re-examinations of those patients who survived are considered, particularly in regard to the following factors: (1) retinal grade, (2) cardiac efficiency, (3) renal

efficiency, (4) symptom grade, and (5) diastolic blood pressure. The second part is a consideration of the incidence of deaths in relation to sex, severity of symptoms and method of treatment.

### Comparison by Symptoms and Signs

In the analysis under this heading, the change was noted, for each patient, between the initial value or grade and that found at a specified time after treatment, in each of the items noted above. The choice of the time interval is of some importance. It is desirable to use as long a period as possible, to give ample time for the results of treatment to become manifest; a long interval also helps to reduce bias, by eliminating from the analysis all patients who die soon after the initial examination, and who therefore may have been too advanced in the disease to benefit from treatment. It also serves to minimize any effects attributable to psychological betterment and unintentional suggestion. On the other hand, increasing the time interval involves omission from the comparison of all the more recent cases. The best compromise is to base the main comparison on the difference between the initial findings and those at the examination most nearly coinciding with the first anniversary of the commencement of treatment, or of sympathectomy.

Data on change of symptom-grade are available for 47 surgical cases (20 male and 27 female) and 42 medical cases (11 male and 31 female), a total of 89 patients. Observations on criteria 1, 2, 3, and 5 (see p. 288) are also on record for most of these cases. Comparisons of changes after three years were also made, but the number of cases was only 41; the findings for the one-year and three-year periods are fully concordant.

Criteria 2, 3, and 4 are on the ABC scale, an arbitrary value of unity being given to each successive step. Retinal grade is 0, 1, 2, 3, and 4, as described earlier; blood pressure differences were measured quantitatively in mm. Hg. In each group of patients the average change in the medically and surgically treated cases was calculated with respect to each criterion, and the probability that the observed difference, if any, might be attributable to chance fluctuations. The combined probability that all the differences with respect to treatment might be chance effects were then calculated. Where this probability is less than 1 : 20 the treatments are taken as giving significantly different results.

*Results of analysis.* The main findings are as follows.

(1) In the *symptom grading*, the surgical cases show a great and decisive superiority over the medical. The details for a 12-months interval are shown in Table III. A positive value in the last

TABLE III

Mean Changes in Symptom Grade after One Year

| Group | Surgical cases | | Medical cases | | Difference between means* |
|---|---|---|---|---|---|
| | No. | Mean improvement | No. | Mean improvement | |
| | | | *Males* | | |
| 1 | 3 | 0·67 grade | 0 | — | — |
| 2 | 4 | 2·00 | 2 | 0·50 | 1·50 |
| 3 A | 5 | 1·80 | 2 | 0·50 | 1·30 |
| 3 B | 2 | 2·00 | 3 | 0·67 | 1·33 |
| 4 | 2 | 1·50 | 1 | 1·00 | 0·50 |
| 5 A | 3 | 1·33 | 0 | — | — |
| 5 B | 1 | 2·00 | 1 | −1·00 | 3·00 |
| | | | *Females* | | |
| 1 A | 3 | 1·33 | 4 | 0·50 | 0·83 |
| 1 B | 1 | 1·00 | 3 | 0·33 | 0·67 |
| 1 C | 3 | 2·00 | 3 | 0·00 | 2·00 |
| 2 A | 1 | 2·00 | 1 | 1·00 | 1·00 |
| 2 B | 3 | 1·00 | 4 | 0·25 | 0·75 |
| 2 C | 5 | 1·20 | 2 | 0·50 | 0·70 |
| 3 A | 3 | 0·67 | 5 | 0·20 | 0·47 |
| 3 B | 2 | 2·00 | 6 | 0·33 | 1·67 |
| 4 | 1 | 0·00 | 2 | 1·00 | −1·00 |
| 5 A | 4 | 1·50 | 1 | 0·00 | 1·50 |
| 5 B | 1 | 1·00 | 0 | — | — |
| Total .. | 47 | 1·43 | 42 | 0·38 | 1·05 |

* A positive value in the last column indicates that the surgical response was more favourable than the medical. The relief of symptoms one year after treatment in the surgical group is on the average superior to the medical.

column means that the surgical cases did better. It will be seen that only in one group (female group 4, with one surgical and two medical cases) is there a minus sign. As might be expected, the combined test of significance shows an infinitesimal probability (less than 1 : 1,000,000,000) that the superiority of the surgical cases is due to sampling fluctuation.

On the average, the surgical cases improved by about 1·4 symptom grades in the course of a year; almost all were able to work, and many were free from symptoms. In the medical cases, the average improvement was less than 0·4 of a symptom grade.

(2) In *diastolic blood pressure*, the medical cases show an average rise while the surgical cases show an average fall, and the difference is highly significant statistically. The amount of rise or fall did not seem to vary with the severity of the cases. It was therefore legitimate to pool all the surgical and all the medical cases. The means and some tests of significance are shown in Table IV. Although

TABLE IV

MEAN CHANGES IN DIASTOLIC BLOOD PRESSURE AFTER ONE YEAR

| Cases | No. | Mean change (mm. Hg.) |
|---|---|---|
| Surgical cases .. | 31 | −8·39 |
| Medical cases .. | 30 | +8·37 |
| Difference .. | | 16·76±5·08 |
| t .. .. | | 3·30 |
| p .. .. | | 0·001 approx. |

the changes are statistically established, they are not very striking in magnitude, averaging +8·4 mm. Hg. in the medical cases and −8·4 mm. Hg. in the surgical.

(3) In the *retinal grading* there was a difference in favour of the surgical cases, which is just statistically significant. On the average the surgical cases improved in twelve months by 0·5 of a grade, while the medical cases showed no change.

(4) & (5) *Cardiac* and *renal gradings* showed a difference in favour of surgical treatment which, however, in neither case was statistically significant.

The general conclusion from this part of the analysis is that among patients who survive a year or more, those who received surgical treatment are functionally and subjectively considerably better than those treated medically. The surgical cases also appear to be better on objective signs, blood pressure, and cardiac, retinal, and renal gradings. But the difference in the well-being of the patients is much greater than would be expected from these objective assessments.

### COMPARISON BY MORTALITY

We now come to the consideration of the second part of the statistical analysis—the analysis of death incidence. Including all surgical cases and the first and second class medical comparisons, we have records of 128 patients, of whom 36 died. It was soon obvious that the death rate in the benign cases (groups 1 to 4 inclusive) was so widely different from that in the malignant cases (groups 5A, 5B, and 5C) that those two classes were best treated separately.

In the *benign* groups there are 45 surgical cases, with 5 deaths, compared with 55 medical cases, with 7 deaths. On the crude figures there is no evidence of any difference. This is confirmed by more refined analysis. These patients were of disparate ages, and had been under observation for periods varying from a few months to several years. The older the patient, and the longer the period under observation, the greater the risk of death. For each patient was calculated the chance of dying during the period of observation if he or she had the same death risk as prevailed for persons of like age and sex in the general population, as listed in the Life Table for Scotland for 1931. The period of risk for survivors was taken as the time since the first examination, and for deceased patients as the period from the first examination until death. The sum of the figures for all the patients in a group gives the number of "expected deaths." The data are shown in Table V.

It will be seen that there were 5 deaths in surgical cases, against the expectation of about 1·1; and 7 in medical cases against the expectation of about 1·3 deaths. This indicates that the death rates for persons with benign essential hypertension seeking hospital advice is about 5 times that prevailing in the population as a whole, and there is no evidence, on these small numbers, of any difference between medical and surgical cases.

### THE MORTALITY RATE IN MALIGNANT HYPERTENSION

Of the original medical group of 20 malignant hypertensive patients, 2 were unsuitable for inclusion in the statistical analysis, one being a third-class comparison already discarded, and the other dying a few days after admission to hospital. There remains for consideration the 10 surgical patients of whom 5 died, and 18 medical patients of whom 17 died. At first sight this suggests a strong recommendation of surgical treatment, but further detail is necessary to ensure that the groups are comparable. All the cases surgically treated were regarded as suitable for operation by both physicians and surgeons with the exception of one patient, a woman who had been in congestive heart failure prior to

TABLE V

DEATHS IN PATIENTS WITH BENIGN HYPERTENSION*

| Group | Surgical cases | | | Medical cases | | |
|---|---|---|---|---|---|---|
| | No. of patients | Deaths | | No. of patients | Deaths | |
| | | Expected | Observed | | Expected | Observed |
| | | | *Males* | | | |
| 1 | 3 | 0·07 | 1 | 3 | 0·06 | 0 |
| 2 | 5 | 0·29 | 0 | 3 | 0·08 | 2 |
| 3 A | 6 | 0·19 | 0 | 2 | 0·04 | 0 |
| 3 B | 2 | 0·02 | 0 | 3 | 0·09 | 0 |
| 4 | 2 | 0·04 | 0 | 2 | 0·03 | 1 |
| All male | 18 | 0·61 | 1 | 13 | 0·31 | 3 |
| | | | *Females* | | | |
| 1 A | 3 | 0·04 | 0 | 4 | 0·07 | 0 |
| 1 B | 1 | 0·01 | 0 | 6 | 0·23 | 0 |
| 1 C | 3 | 0·09 | 0 | 5 | 0·16 | 1 |
| 2 A | 2 | 0·02 | 0 | 2 | 0·05 | 0 |
| 2 B | 4 | 0·08 | 1 | 4 | 0·07 | 0 |
| 2 C | 7 | 0·16 | 2 | 5 | 0·12 | 0 |
| 3 A | 3 | 0·06 | 1 | 5 | 0·08 | 1 |
| 3 B | 3 | 0·05 | 0 | 7 | 0·23 | 0 |
| 4 | 1 | 0·02 | 0 | 4 | 0·04 | 2 |
| All female | 27 | 0·51 | 4 | 42 | 1·02 | 4 |
| Total .. | 45 | 1·12 | 5 | 55 | 1·33 | 7 |

* By comparing the expected deaths with the observed, the death rate in benign hypertension is approximately five times that prevailing in the population as a whole. There is no significant difference between our two groups of medically and surgically treated patients.

admission to hospital. In this case the surgeons were reluctant but were finally persuaded to intervene.

The medically treated cases were graded in three categories: (A) where there was no contraindication to surgical treatment; (B) where the physicians thought operation justifiable although one criterion fell short of the desirable level; and (C) cases where neither physicians nor surgeons would advise operation, that is with severe renal or cardiac failure or both combined.

The surgical cases described above fell into category (A) with the exception of the one stated, who was graded (B). Details of the cases in these surgical and medical categories are given in Table VI.

It will be seen that of the 9 surgical (A) cases, 5 died after an average period of 13 months and 4 have lived for an average of 26 months after being first treated. There are 5 medical (A) cases all of whom died after an average interval of 5 months. The only surgical (B) case has not died after an interval of 14 months; out of 9 medical (B) cases, 8 died after an average of 1·8 months, and one has survived for the short period of 3·5 months. The 4 medical (C) cases died after an average interval of 1·3 months.

The only valid control for the main body of surgical malignant cases is the (A) group of medical patients. As far as they go the comparative death rates in (A) and (B) categories appear to favour surgical treatment. The data however are insufficient for a definite decision. The physicians in charge of the medical (A) cases are of the opinion, on clinical grounds, that these patients would have lived longer had they been treated surgically; but for statistical purposes a much larger series of malignant cases is required. It seems unlikely that this will be obtained in cases fit enough for operation, because this will not be refused in future merely in order to provide a control group. But there is a prospect of an entirely ethical future experiment. In the (B) cases, where the physicians believe operation would be beneficial and the surgeons regard it as too hazardous, the opinion of the surgeons has hitherto usually prevailed. If it could be agreed that in future half these cases, chosen by a random process, could be operated on, and the other half kept as controls, decisive information about the value of operation in the most severe cases might be forthcoming. Since in the absence of surgical treatment these patients have an

TABLE VI

DEATHS IN PATIENTS WITH MALIGNANT HYPERTENSION

*(A) No contraindication to surgical treatment*

| | Died | | | | Survived | | | |
|---|---|---|---|---|---|---|---|---|
| | Group | Sex | Age | Months lived | Group | Sex | Age | Months observed |
| Surgical (9 cases) | 5 A | M | 46 | 9 | 5 A | M | 44 | 18 |
| | 5 B | M | 61 | 10 | 5 A | M | 47 | 50 |
| | 5 C | M | 45 | 5 | 5 A | F | 45 | 22 |
| | 5 A | F | 36 | 13·5 | 5 A | F | 45 | 14 |
| | 5 A | F | 45 | 29 | | | | |
| | 5 cases | | | Mean 13·3 | 4 cases | | | Mean 26·0 |
| Medical (5 cases) | 5 A | M | 40 | 1 | | | | |
| | 5 A | M | 44 | 2 | | | | |
| | 5 B | M | 60 | 6 | | | | |
| | 5 A | F | 57 | 12 | | | | |
| | 5 A | F | 31 | 5 | | | | |
| | 5 cases | | | Mean 5·2 | | | | |

*(B) One criterion against surgical treatment*

| | Died | | | | Survived | | | |
|---|---|---|---|---|---|---|---|---|
| | Group | Sex | Age | Months lived | Group | Sex | Age | Months observed |
| Surgical (1 case) | | | | | 5 B | F | 44 | 14 |
| Medical (9 cases) | 5 A | M | 49 | 5 | 5 C | M | 56 | 3·5 |
| | 5 A | M | 50 | 2 | | | | |
| | 5 A | M | 66 | 0·5 | | | | |
| | 5 A | M | 54 | 1 | | | | |
| | 5 B | M | 53 | 1 | | | | |
| | 5 C | M | 64 | 3 | | | | |
| | 5 A | F | 48 | 1 | | | | |
| | 5 B | F | 49 | 1 | | | | |
| | 8 cases | | | Mean 1·8 | 1 case | | | 3·5 |

*(C) Severe cardiac or renal failure*

| | Group | Sex | Age | Months lived |
|---|---|---|---|---|
| No surgical cases | | | | |
| Medical (4 cases) | 5 A | M | 51 | 0·3 |
| | 5 C | M | 53 | 0·5 |
| | 5 C | M | 48 | 3 |
| | 5 B | F | 56 | 1·5 |
| | 4 cases | | | Mean 1·3 |

average expectation of life of less than two months, no harm can be done by operation, and possibly some good to the patients, as well as providing an advance in knowledge.

In malignant hypertension surgical treatment seems to lead to greater well-being in surviving patients on a larger scale than would be deduced from the concomitant small remission of objective findings. There are indications, falling short however of statistical significance, that the risk of death may be lowered by operation. Valuable evidence could probably be obtained if operation were performed on alternate cases for which physicians recommend operation and surgeons disagree.

## Summary and Conclusions

One hundred and fifty-one patients, suffering from essential hypertension, form the basis of the present study. They have been carefully investigated and their progress observed over a number of years.

For comparative purposes they have been divided into two groups. The first, numbering 96 patients, received purely medical treatment—rest and sedation. The second group, composed of 55 patients, was submitted to sympathectomy.

Largely as a result of changing standards regarding the indications for surgical intervention and with widening experience of the procedure over the past nine years, it has been possible retrospectively to match our surgical group in their pre-operative state with a corresponding series of medical cases in whom for one reason or another surgery was not employed.

By subdividing the medical and surgical cases into smaller categories alike in sex, age, retinal state, cardiac and renal function, and diastolic blood pressure, as determined before the start of therapy, accurate comparison was facilitated and the findings observed a year later in each group reassessed. The results thus obtained have been submitted to statistical analysis. For a variety of reasons 22 medical cases were found unsuitable for comparison and were discarded.

The statistical investigation indicates that in benign hypertension at the end of one year and also at the third anniversary of surgical treatment the sympathectomized patients experience a greater relief of symptoms than corresponding medical groups. Almost all in the surgical group were able to work and many were free from symptoms.

By the end of a year the diastolic blood pressure showed on the average a fall of approximately 8 mm. Hg. in the surgical group, whereas amongst those patients treated exclusively by medical measures it had tended to rise by about an average of 8 mm. after the same length of time. In the surgical group there was also a slight improvement in the retinal grade. In this respect the medical cases showed no change.

The general conclusion is that when our two groups are compared those patients who receive surgical treatment for their benign hypertension are subjectively considerably better than those treated medically. There is less change in the level of the diastolic pressure.

The death rate for persons whose symptoms of so-called benign hypertension lead them to seek help in the hospital is about five times that prevailing in the population as a whole. From our small numbers submitted to analysis there is no evidence of any difference in the mortality rates in the two groups of medically and surgically treated patients.

In malignant hypertension, the data available from a comparatively small number of patients—30 in all—suggest that surgery leads to greater well-being in survivors, but a much larger series is required if statistical proof is to be obtained.


We gladly express our warmest thanks to our surgical colleagues, Prof. Norman Dott, Prof. Sir James Learmonth, and Mr. George Alexander, who by their generous cooperation have made the present investigations possible. Dr. Sven Hammarström of Stockholm has kindly placed some as yet unpublished observations at our disposal.

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# SOCIÉTÉ EUROPEENNE DE CARDIOLOGIE

The following communication from the Société Européenne de Cardiologie (European Cardiological Society) is printed for the information of the members of the British Cardiac Society. It has not yet been considered by the British Cardiac Society or by its Council and its publication is for information and must not be taken as meaning that the details have been accepted.

Le 29 janvier 1949 se sont réunis à Buxelles des cardiologues, représentant quatorze nations européennes, dans le but de constituer la Société Européenne de Cardiologie.

Les statuts provisoires suivants ont été adoptés:

(1) La Société Européenne de Cardiologie se propose do grouper les cardiologues de toutes les nations d'Europe.

(2) La Société Européenne de Cardiologie a pour but de contribuer au développement de la cardiologie, de favoriser la collaboration scientifique, d'aider aux rapprochements personnels. Dans le domaine de la pratique cardiologique la Société Européenne de Cardiologie peut être amenée à donner des directives d'ordre moral.

(3) La direction de la Société sera assurée par:

(*a*) Un Bureau composé d'un Président d'honneur, d'un Président, de trois Vice-Présidents, d'un Secrétaire général et d'un Trésorier:

(*b*) Un Comité constitutif composé des délégués officiels réunis à Bruxelles à l'assemblée constitutive. Ce Comité pourra être élargi ultérieurement.

(4) Une réunion du Bureau et du Comité constitutif aura lieu au moins tous les deux ans. Toutefois, le Président a pouvoir de prendre toute décision d'urgence pourvu qu'il ait recueilli l'approbation écrite de la majorité des membres du Comité constitutif.

(5) La Société comprendra des membres titulaires, correspondants et honoraires.

(6) Tout cardiologue européen peut faire partie de la Société pour autant que sa candidature ait été parrainée par la Société à laquelle il appartient, à son défaut par son délégué national, à son défaut par un membre du Comité constitutif.

(7) Pour entretenir les rapports entre les membres et étendre l'action de la Société Européenne de Cardiologie, le Comité organisera, en principe, tous les deux ans, un Congrès. Il s'intercallera entre les réunions de l'Association Pan-Américaine de Cardiologie.

(8) Le Bureau et le Comité constitutif ont l'autorisation de chercher les appuis financiers nécessaires pour subvenir aux activités courantes, pour organiser des réunions scientifiques, etc.

(9) Le nouveau groupement devra, en temps voulu, avec la Société Pan-Américaine de Cardiologie, former la Société Internationale de Cardiologie.

(10) Toute question non envisagée dans ces statuts sera traitée dans le règlement d'ordre intérieur.

Bruxelles, le 29 janvier 1949.

# EUROPAN CARDIOLOGICAL SOCIETY

On January 29, 1949, a meeting took place at Brussels between delegates of fourteen European countries in order to constitute a European Cardiological Society.

The following provisional *by-laws* have been agreed:

(1) The European Cardiological Society proposes to group the cardiologists of all the European nations.

(2) The aims of the European Cardiological Society are to foster the development of cardiology, to further scientific exchanges and to help personal contacts of those working in this speciality. The European Cardiological Society may also be called upon to give moral directives in the sphere of practical cardiology.

(3) The administration of the Society will be entrusted to:

(*a*) A Council consisting of an Honorary President, a President, three Vice-Presidents, a General Secretary and a Treasurer;

(*b*) A Constitutive Committee consisting of the official delegates present at the constitutive Assembly in Brussels. This Constitutive Committee may be enlarged at a later date.

(4) A meeting of the Council and the Constitutive

Committee will take place at least biennially. In case of emergency, however, the President has authority to take the necessary decisions without a meeting, providing he has obtained the written agreement of the majority of the Constitutive Committee.

(5) The Society will consist of active members, corresponding members, and honorary members.

(6) Membership of the Society is open to all European cardiologists providing their admission is recommended by the Society to which they belong or by their national delegate or by a member of the Constitutive Committee.

(7) It is suggested that, if possible, a biennial Congress will be organized in order to maintain close collaboration between the members and enlarge the Society's activities. These Congresses will be held at intervals between those of the Pan-American Cardiological Association.

(8) The Council and the Constitutive Committee of the Society have authority to seek financial assistance to cover the necessary expenditure inherent to current activities, the organization of scientific meetings, and any other purposes decided by Committee.

(9) The new Society will, in due course, together with the Pan-American Cardiological Society, form the International Cardiological Society.

(10) All matters not dealt with in the present *By-Laws* will be subject to Regulations.

Brussels, January 29, 1949.

*Great Britain:*
(s.) D. Evan Bedford.

*Holland:*
(s.) Formijne.

*Belgium:*
(s.) Pierre Rylant; François van Dooren.

*Italy:*
(s.) Camillo Colombi.

*Denmark:*
(s.) Kaj Larsen.

*Norway:*
(s.) Hakon Rasmussen.

*Spain:*
(s.) Antonio Crespo-Alvarez. Trias de Bes.

*Portugal:*
(s.) Eduardo Coehlo.

*Finland:*
(s.) Pentti Halonen.

*Sweden:*
(s.) Gustav Nylin; Gunnar Biorck.

*France:*
(s.) Charles Laubry; Jean Lenegre.

*Switzerland:*
(s.) Ivan Mahaim.

*Greece:*
(s.) Demosthène Papapanayotou.

*Jugoslavia:*
(s.) Cedomil Plavsic.

The *provisional Council of the European Cardiological Society* is constituted as follows:

*Honorary President:*
Professor Charles Laubry (France).

*President:*
Professor Gustav Nylin (Sweden).

*Vice-Presidents:*
Doctor D. Evan Bedford (Great Britain).
Professor Jean Lenegre (France).
Professor Eduardo Coehlo (Portugal).

*General Secretary:*
Doctor François van Dooren (Belgium).

*Treasurer:*
Doctor Ivan Mahaim (Switzerland).

# ABSTRACTS OF CARDIOLOGY

**Cholesterol and Myocardial Infarcts.** H. LALIBERTÉ and M. VACHON. *Laval méd.*, **13**, 294–302, March, 1948.

Cardiac infarction may occur in a young man or woman, in whom there is no evidence of syphilis or hypertension. The authors discuss 39 such cases in patients varying in age from 28 to 47, 11 of whom were women and 28 men, and in which the ultimate cause of the infarct was thought to be fatty deposits in the small arteries due to a raised blood cholesterol. In hereditary xanthomatosis there is a disturbance of the lipid metabolism, and, although fatty deposits in skin and mucous membrane are not always seen, abdominal angina and infarcts sometimes occur; there is always a raised blood-cholesterol in such cases. In 7 cases of cardiac infarction, the only common factor was a high level of cholesterol in the blood. In only 2 cases was necropsy possible; in both there was an extensive infarct of the left ventricle, the arteries being stuffed with yellow plaques with little sign of fibrosis. All patients had a normal blood pressure, and most had had previous attacks of præcordial or abdominal pain. The authors conclude that the sterols play an important, perhaps a primary, role in the causation of arterial occlusion. *T. E. C. Early*

**Clinical Features in Coarctation of the Aorta: A Review of 96 Cases.** N. A. CHRISTENSEN and E. A. HINES. *Proc. Mayo Clin.*, **23**, 339–342, July 21, 1948.

At the Mayo Clinic between 1925 and 1947 coarctation of the aorta was diagnosed in 119 cases. Males predominated over females in the ratio 3·8 to 1. Only 26% of the patients were below 20 years of age—the period of life when surgery is best tolerated. In 30% the condition was discovered incidentally; high blood pressure frequently pointed to its presence, but only 3 patients gave a history of intermittent claudication. Palpation of the larger arteries to detect differences in pulsation is more reliable than the smaller limb arteries. Differences in arterial pulsation and pulse pressure in the arms may aid in locating the site of the coarctation. In 80% there was evidence of collateral circulation over the scapular and interscapular regions, and somewhat less frequently over the supraclavicular and internal mammary regions.

Cardiovascular murmurs were present in 94%, the most frequent being a fairly loud systolic bruit over the base of the heart. Basal diastolic murmurs were heard in 20% and were probably associated with valvular lesions. In 25% there was *x*-ray evidence of cardiac enlargement and in 30% electrocardiographic evidence of left ventricular preponderance. Ophthalmoscopic examination showed general narrowing of the retinal arterioles, particularly in the cases with hypertension, but no patient had hypertensive retinopathy. Renal function studies revealed no abnormality and this possibly accounts for the absence of severe hypertensive disease. Important features in establishing the diagnosis were found to be: (1) characteristic differences in arterial pulsations and in direct and indirect blood pressure readings between the upper and lower limbs; (2) evidence of well developed collateral circulation; (3) rib notching in the presence of one or more cardiac or cardiovascular murmurs.

*H. E. Holling*

**The Treatment of Angina Pectoris with Propylthiouracil.** G. HOLLANDER and H. MANDELBAUM. *Ann. intern. Med.*, **28**, 1150–1156, June, 1948.

Ten patients with angina pectoris and hypertension were treated with propylthiouracil in the Jewish Hospital, Brooklyn, N.Y. Initially a dose of from 50 to 100 mg. was given daily; this was increased to a maximum of 200 mg. daily. Improvement took place within 8 weeks in 4 of these patients, and 2 of them were able to resume work. Two became progressively worse during treatment. No correlation could be found between the levels of the basal metabolic rate and improvement in symptoms. One case with an initial figure of −8% became free from attacks when the level fell to −26%; 3 more cases, in which the initial levels were raised, improved while the rate was still above normal limits. The blood cholesterol levels often did not rise as the basal metabolic rate fell. No toxic effects on the blood were observed, but water retention occurred in 7 patients, causing dyspnœa and œdema of the legs. *C. W. C. Bain*

**Experiences with the Use of Heparin and Dicumarol in the Treatment of Coronary Thrombosis and Thromboembolic Disease.** J. B. VANDER VEER, D. S. MARSHALL and P. T. KUO. *Trans. Stud. Coll. Phys. Phila.*, **16**, 67–72, June, 1948.

The authors, working in the Pennsylvania Hospital, Philadelphia, have participated in a controlled study sponsored by the American Heart Association to determine the value of dicoumarol therapy in coronary occlusion with myocardial infarction. There were 35 treated cases and 51 controls. Prothrombin times were kept so far as was possible between 30 and 35 seconds, control times being 13 to 15 seconds. The initial dose of dicoumarol was 300 mg. daily for 2 or 3 days, the maintenance dose somewhat less than 100 mg. daily; treatment was continued for about a month. Among the controls thrombo-embolic complications occurred in 12 patients, 9 of whom died; there were also 9 deaths from other causes. In the treated cases thrombo-embolic complications occurred in 6 with a fatal ending in 2; there was 1 other death.

The results of a preliminary analysis of the first 800 cases of cardiac infarction treated with dicoumarol which were collected by a special committee of the American Heart Association are also given. The death rate in the controls was 23%, in dicoumarol-treated cases 13%. Thrombo-embolic complications occurred in 19% of the untreated and in 9% of the treated patients. Hæmorrhagic manifestations of one type or another were encountered in 4% of the controls and in 11% of the treated cases; but serious hæmorrhage was rare.

The value of anticoagulants in the treatment of simple phlebothrombosis or thrombophlebitis is again stressed. In 23 untreated cases there were 9 deaths; in 30 cases treated by venous ligation, 3 deaths; in 49 cases treated with heparin and dicoumarol there was only 1 death. It is admitted that selection of cases was weighted against the controls. *Paul Wood*

**Left Vocal Cord Paralysis Associated with Cardiac Disease.** D. A. DOLOWITZ and C. S. LEWIS. *Amer. J. Med.*, **4**, 856–862, June, 1948.

The literature on the mechanism of paralysis of the left recurrent laryngeal nerve in cases with cardiac enlargement is reviewed, and 2 personal cases are described. One patient had mitral and aortic valvular disease with marked enlargement of the left auricle; the other had atrial septal defect, possibly with mitral stenosis (Lutembacher's syndrome) and greatly enlarged pulmonary conus. The area bounded by the aortic arch superiorly, the pulmonary artery inferiorly, and the ligamentum arteriosum medially was carefully examined in 5 fresh and 22 fixed cadavers, and a group of three to four lateral tracheo-bronchial lymph nodes was constantly found in close proximity to the left recurrent nerve. It is pointed out that these lymph nodes may effectively compress the nerve when accompanied by cardiac hypertrophy, engorgement of the pulmonary artery, or both. *A. Schott*

**Comparison of the Fick and Dye Injection Methods of Measuring the Cardiac Output in Man.** W. F. HAMILTON, R. L. RILEY, A. M. ATTYAH, A. COURNAND, D. M. FOWELL, A. HIMMELSTEIN, R. P. NOBLE, J. W. REMINGTON, D. W. RICHARDS, N. C. WHEELER, and A. C. WITHAM. *Amer. J. Physiol.*, **153**, 309–321, May, 1948. 2 figs., 17 refs.

Cardiac output can be determined from the time-concentration curve in arterial blood (obtained from rapid serial samples) of a dye injected rapidly into a vein. This and the direct Fick method (cardiac catheterization) were compared in 48 almost simultaneous determinations in 31 subjects, including normal subjects at rest and during light and heavy exercise and patients suffering from various cardio-respiratory disease at rest and during occasional light exercise. The technique of determining cardiac output by the dye injection method is described in detail. The results agreed within 25% in all but 6 determinations. The distribution of results about the line of identity was symmetrical, so that the averages for each method were almost identical. The dye method, owing to its rapid performance and its nature, is more apt to reflect physiological variations. The sources of error in it are discussed, the chief being recirculation of blood (containing dye) during the determination.

*R. A. Gregory*

**The Phenomenon of Skin Hyperalgesia in Angina Pectoris.** E. V. LEVINSON. *Klin. Med., Mosk.*, **26**, No. 9, 47–55, 1948.

In 145 patients with anginal pain, areas of cutaneous hyperalgesia were repeatedly mapped out with a view to evaluating their diagnostic significance and their relation to the results of treatment. Cutaneous hyperalgesia was most commonly present in the C2 to C4 and D1 to D5 dermatomes, rarely in the C5 to C7 and D6 dermatomes. These zones were not static in any one patient but were liable to change if the irradiation of the pain changed. They were always present in patients whose attacks were frequent or prolonged, but were only found in 79% of the whole series. When patients were tested within 3 days of an attack, areas of hyperalgesia were present in 93%. Their disappearance is considered to be a valuable index to the success of treatment. *S. S. B. Gilder*

**Studies on the Blood Flow in the Extremities in Cases of Coarctation of the Aorta: Determinations Before and After Excision of the Coarctate Region.** K. G. WAKIM, O. SLAUGHTER, and O. T. CLAGETT. *Proc. Mayo Clin.*, **23**, 347–351, July 21, 1948.

Plethysmographic measurements of the blood flow to the arm and leg in 14 normal persons at rest and 14 patients with aortic coarctation revealed no significant difference between the two groups, and in 9 cases no change in blood flow followed surgical removal of the coarctation. *H. E. Holling*

**The Relationship of Retinal Hemorrhages in Hypertensive Patients to Cerebral Hemorrhage. A Comparison of the Retinal Picture in Hypertensive Individuals who Died of Heart Failure with those who Suffered a Cerebral Hemorrhage.** L. A. SOLOFF and C. T. BELLO. *Amer. J. med. Sci.*, **215**, 660–664, June, 1948.

Cerebral hæmorrhage is the cause of death in nearly one-third of hypertensive individuals. The final mechanism of the hæmorrhage is ill understood. It has been ascribed to the development of miliary aneurysms, to ischæmia of brain tissue and weakening of support for the blood vessels, to disease and rupture of the walls of veins, and, more recently, to capillary weakness. The latter factor has been associated with the occurrence of retinal hæmorrhage.

On a re-investigation, retinal hæmorrhages were found to have been present in 5 out of 17 patients who had had a cerebral hæmorrhage; retinal hæmorrhage was present in 14 out of 18 patients with hypertension who died of cardiac failure without cerebral hæmorrhage. Retinal hæmorrhages occurred more frequently in patients with large areas of "spasm" of the retinal arteries than in subjects with marked thickening of these vessels. It is

concluded that retinal hæmorrhages cannot be used as a prognostic sign of future cerebral hæmorrhage.

*J. McMichael*

**True Aneurysms of the Mitral Valve in Subacute Bacterial Endocarditis.** O. SAPHIR and E. P. LEROY. *Amer. J. Path.*, **24**, 83–95, Jan., 1948.

Mycotic aneurysms of the mitral valve were found in 5 out of 12 cases of subacute bacterial endocarditis treated with sulphonamide preparations, heparin, or penicillin. These cases were observed between 1943 and 1946; the authors were unable to find an example of mycotic aneurysm formation in 41 cases of subacute bacterial endocarditis seen between 1935 and 1943. Rupture of the aneurysm occurred in 4 cases, and the increased incompetence of the mitral valve may have contributed to death. The aneurysms probably arise in areas of granulation tissue situated in the substance of the valve. The authors suggest that the aneurysms represent attempts at healing of the endocarditis, perhaps as a result of the increasing use of chemotherapeutic agents in recent years.

*R. H. D. Short*

**The Action of Neostigmine in Supraventricular Tachycardias.** S. WALDMAN and L. PELNER. *Ann. intern. Med.*, **29**, 53–63, July, 1948.

The action of neostigmine methylsulphate (or "prostigmin") on sinus tachycardia and auricular and nodal paroxysmal tachycardias is discussed; the paper includes case notes and electrocardiograms of 5 patients. The tracings demonstrate the slowing of sinus tachycardias with rates of about 130 per minute to about 80 per minute within about 20 minutes of the injection of 1 mg. of neostigmine, and the restoration of normal rhythm in a case of auricular tachycardia and in one of nodal tachycardia 5 minutes after injection. Immediately on the return of sinus rhythm the P–R interval is prolonged, but becomes normal within a few minutes. In another case of auricular tachycardia the abnormal rhythm persisted after the injection, but there was an immediate and progressive effect on A-V conduction, so that, 33 minutes after the injection, there was 3 : 1, 4 : 1 A-V block. Two days later normal rhythm was recorded.

The influence of neostigmine on these types of tachycardia is believed to be due to its action on the myoneural junctions of parasympathetic vagus fibres in the S-A and A-V nodes and in auricular muscle. The drug augments vagus activity at these sites by inhibiting the action of cholinesterase. If these tachycardias result from the action of sympathomimetic amines on the heart, the use of the parasympathomimetic drug, neostigmine, is rational therapy.

*S. H. Cookson*

**Continued Hypertension. Prognosis for Surgically Treated Patients.** R. H. SMITHWICK. *Brit. med. J.*, 2,237–243, July 31, 1948.

It is necessary to turn to the U.S.A. for any large series of patients treated surgically for hypertension; the author describes his second series in this paper. The operations were performed in Boston, Massachusetts, and the author's own lumbo-sacral technique was employed. All of the 256 patients were suffering from continuous essential or malignant hypertension and had been operated upon at least 5 and at the most 9½ years previously.

The state of the cardiovascular system was evaluated before and after operation with particular reference to the cerebral, retinal, cardiac, and renal areas. Intravenous pyelography was carried out as a routine, and the blood pressure data were so far as possible obtained in a standard fashion. Male patients comprised 39·4% and females 60·6% of the series. The total mortality during the 5 to 9 year period of observation was 31%, the mortality among males being 34% and among females 29%. The causes of death were cerebral, cardiac, renal, and miscellaneous, in that order, with a heavy preponderance in the very young and the older age groups. The prognosis became poorer as the degree of eyeground abnormality increased, and the same applied to the cardiovascular findings. The presence of arteriosclerosis was associated with a particularly poor prognosis. It had been previously noted that in a follow-up period of 1 year to 5 years the blood pressure levels were lowered significantly in the majority of unselected patients, but in the period of 5 to 9 years this lowering is not maintained and there has been a return of the pressure to pre-operative levels in 44% of cases. There was evidence, however, of the slowing up of the rate of progress of cardiovascular disease, and this may prove to be a very important accomplishment. Comparison with medical treatment is made as much as possible, but the major handicap is the absence of reliable and adequate medical statistics. Such comparisons as can be made at this time, while admittedly inadequate, suggest that surgical treatment has favourably altered the prognosis in many cases of continued hypertension and cardiovascular disease.

*H. T. Simmons*

**Asynchronous Activity of the Dog's Heart After Section of the Right Branch of the Bundle of His.** A. I. SMIRNOV. *Arkh. Patol.*, **10**, No. 3, 7–13, May–June, 1948.

The influence of section of the right branch of the bundle of His on the action of the heart was observed over a period of 6 years in a dog. During the first days after the operation a reduplicated first heart sound became audible at the apex. Three weeks later a systolic murmur became audible over the whole thorax. This murmur disappeared just before the death of the dog.

Six weeks after the operation atypical lævocardiograms were present in leads II and III, indicating that the right bundle of His had been severed. Repeated X-ray examination showed a gradual dilatation of the right ventricle. Changes in the electrocardiogram developed slowly after the operation. During the last days before the dog died of heart failure a marked œdema and ascites developed. Post-mortem examination showed that the right branch of the bundle of His had been correctly cut and that its ends had not united again. Hypertrophy and degeneration of the right myocardium and a relative tricuspid incompetence were found. The

compensation of the right ventricle (hypertrophy and dilatation) had succeeded in maintaining normal circulation over a period of 4 years. This compensation, however, failed after 6 years, causing death of the animal. No synchronous rhythm with the left ventricle occurred during the 6 years after the operation.

*J. Flaks*

**Serum Protein in Cardiac Patients.** G. BIÖRCK, S. HEDLUND, J. KARNELL, and H. KARNI. *Nord. Med.*, **38**, 1179–1182, June 11, 1948.

The authors report the results of serum protein estimations on 147 hospital patients with various forms of heart disease. Globulin is rarely reduced but albumin is in two-thirds of the cases, especially if there is heart failure, œdema, or evidence of liver disease as shown by the other usual tests. Owing, however, to the multiplicity of factors governing the concentration of protein in the blood (absorption, utilization, synthesis, dilution, and loss) and the fact that most of these factors are affected in some way by cardiac decompensation, interpretation is very difficult.

In recovery from heart failure, the albumin content increases as does also the erythrocyte sedimentation rate, possibly due to a rapid increase in fibrinogen. These increases are thought to be due to improvement in liver function and appear to be little related to diet, though the authors recommend use of protein hydrolysates. They admit however that no increase in the serum proteins may be detectable while decompensation persists and stress the importance of not giving hydrolysates, which contain an appreciable amount of salt.

*A. M. M. Wilson*

**Serum Cholesterol Values in Cardiac Patients.** G. BIÖRCK and H. KARNI. *Nord. Med.*, **38**, 1175–1179, June 11, 1948.

The authors discuss the value of cholesterol estimations in patients with heart disease, based on the estimations carried out on 314 patients in the cardiac clinic of the Södersjukhus in Stockholm. Sackett's modification of Bloor's method was used.

The values varied considerably within an age group or disease group and even in the same patient at different times, but on the whole values were higher in women than in men, in old people than in young ones, and in patients with cardiac sclerosis than in those with other types of heart disease. The level tended to fall after admission to the ward irrespective of the diagnosis. The authors conclude, in agreement with Josephson (*Nord. Med.*, 1947, **33**, 498), that a single estimation is almost useless and that though repeated ones may be of diagnostic assistance in cases of liver disease, essential hypercholesterolæmia, and thyroid disease, they are of very doubtful value in the differential diagnosis of cardiovascular conditions.

*A. M. M. Wilson*

**Carotid Artery Thrombosis: Report of Eight Cases due to Trauma.** H. W. CALDWELL and F. C. HADDEN. *Ann. intern. Med.*, **28**, 1132–1142, June, 1948.

The authors describe 8 cases of carotid artery thrombosis seen in a military hospital in 1945. The thrombosis was due to trauma of the common carotid following penetrating wounds of the neck. Patients were usually comatose on admission to hospital, with changes in the pupil reactions on the affected side and signs of hemiplegia on the other. Absence of pulsation over the temporal artery from involvement of the external carotid was found to be a valuable confirmatory sign. One patient recovered after heparin was administered; the remainder died. There were 5 necropsies; in 1 case the thrombus had extended as far as the circle of Willis; in 2 cases major cerebral vessels were blocked by emboli. The authors consider that this condition may be more common in war surgery than has been supposed.

*C. W. C. Bain*

**Chronic Infection and Atherosclerosis. Some Additional Experimental Data.** N. W. JONES and A. L. ROGERS. *Arch. Path.*, **45**, 271–277, March, 1948.

There is some clinical and experimental evidence that chronic infections, especially of the gall-bladder and paranasal sinuses, may play a part in the causation of atherosclerosis and associated heart failure. Micro-organisms were found in sections of the thickened, thrombosed small arteries of chronically hyperplastic sinus tissues removed at operation. Similar organisms were sometimes demonstrated in sections of thrombosed coronary arteries from patients dying of acute coronary thrombosis. Micro-organisms introduced into the paranasal sinuses or paralaryngeal lymph nodes of cats could be demonstrated in the walls of the aorta and coronary arteries. Trypan-blue granules introduced into the paralaryngeal lymph nodes were demonstrated in phagocytic cells within the walls of the aorta and coronary arteries.

*Martin Hynes*

**Effect of Choline in the Prevention of Experimental Aortic Atherosclerosis.** A. STEINER. *Arch. Path.*, **45**, 327–332, March, 1948.

Rabbits were given 1 g. of cholesterol with their food three times weekly. A well-controlled experiment showed that the addition to the diet of 0·5 or 1 g. of choline hydrochloride daily delayed the development of atherosclerosis for 80 days or more. The effect was greater with the larger dose of choline. Hypercholesterolæmia was equal in the control animals and in those receiving choline.

*Martin Hynes*

**Vitamin E in Heart Disease.** H. LEVY and E. P. BOAS. *Ann. intern. Med.*, **28**, 1117–1124, June, 1948.

Vitamin E (α-tocopherol) was given without benefit to 13 patients suffering from heart disease with relatively fixed symptoms. The series comprised cases of angina pectoris and cardiac failure due to coronary disease or rheumatic valvular disease. The drug was given in doses varying between 200 and 800 mg. daily and administration was continued for from 7 to 12 weeks. In one case of angina pectoris there was a temporary improvement for the first two weeks, but the attacks then

continued at their former frequency. In no other case was the number of anginal attacks affected, nor did any of the signs abate in those with cardiac failure. The authors conclude that the use of vitamin E in heart disease is not warranted. *C. W. C. Bain*

**The Effect of Dicumarol on the Heart in Experimental Acute Coronary Occlusion.** H. L. BLUMGART, A. S. FREEDBERG, P. M. ZOLL, H. D. LEWIS, and S. WESSLER. *Amer. Heart J.*, **36**, 13–27, July, 1948.

The administration of dicoumarol does not retard the healing process or the development of collateral circulation in dogs with experimentally produced myocardial infarction. *R. T. Grant*

**Coronary Deaths in "Healthy" Young Soldiers: A Clinicopathologic Study.** N. E. REICH. *Amer. Practit., Phila.*, **2**, 731–747, July, 1948.

Coronary artery disease as a cause of death in young subjects received little attention until the war of 1939–45. The present article deals with findings in 11 "healthy" soldiers, ranging in age from 22 to 38 years, who died from coronary artery disease. These men had been subjected to frequent medical examination, but the results were negative. In 7 over-weight was thought to be a predisposing factor; the effects of alcohol and tobacco were considered to be negligible. The symptoms were generally atypical in those patients surviving more than an hour. Pain was present in the epigastrium, left chest, or præcordium. Usually it did not radiate, although in one case there was continuous pain in the jaw for 3 days and in another left shoulder pain. Contrary to accepted ideas, the onset of pain was always in the waking hours, and pain was not associated with any strenuous activity. Six of the patients died within an hour, and 5 lived for from 2 to 33 days. At necropsy half of the cases showed significant cardiac hypertrophy. Severe coronary sclerosis was present in 6 of 8 cases with actual thrombosis, and was moderate in 2 others. Two patients had sclerosis without thrombosis and in one there was a coronary embolism with arteritis and septic thrombosis of the smaller coronary branches.
*James W. Brown*

**Excessive Hypertension of Long Duration.** A. M. BURGESS. *New Engl. J. Med.*, **239**, 75–79, July 15, 1948.

From patients seen in private consultation since 1914, 100 consecutive patients were selected in whom hypertension (systolic pressure greater than 180 or diastolic pressure greater than 100) had existed for more than 8 years. Of the 100 patients 32 were between 28 and 50 years of age, 39 between 51 and 60, and the remaining 29 between 61 and 77. The shortest duration of hypertension was 9 years, the longest 25 years. In 1947, 53 patients were dead, 30 were in good health, 17 were incapacitated to a greater or lesser degree. The effects of sex, age, height of systolic and diastolic pressures had little effect on the actual duration of life.

This study emphasizes the good prognosis in uncomplicated, benign or non-progressive hypertension.
*W. T. Cooke*

**Preoperative and Postoperative Studies of Intraradial and Intrafemoral Pressures in Patients with Coarctation of the Aorta.** G. E. BROWN, O. T. CLAGETT, H. B. BURCHELL, and E. H. WOOD. *Proc. Mayo Clin.*, **23**, 352–358, July 21, 1948.

Intraradial and intrafemoral pulse waves were recorded by means of a hypodermic strain gauge manometer in a series of patients with coarctation of the aorta. The characteristic findings were an increase in the systolic and diastolic pressures in the radial arteries, and a reduced systolic, though often with an increased diastolic, pressure in the femoral artery. The onset of the femoral pulse wave is often delayed. When the stenosed portion of the aorta was resected and an end-to-end anastomosis carried out the findings reverted to normal, but when the stenosed portion was excised and the subclavian artery anastomosed with the distal aorta the delay in the femoral pulse wave disappeared though the femoral pulse pressure was still reduced. The findings could not be correlated with the clinical response of the patient to the procedure.
*H. E. Holling*

**The Surgical Treatment of Coarctation of the Aorta.** O. T. CLAGETT. *Proc. Mayo Clin.*, **23**, 359–360, July 21.

Between 10 and 20 years of age is regarded as the most suitable age for operation in cases of coarctation of the aorta. Before the age of 10 the aorta is not large enough for satisfactory anastomosis and it is not known whether the ring of scar tissue left in the aorta at the site of the anastomosis will increase in size as normal growth and development take place. Above the age of 20 considerable vascular damage may have occurred and good results cannot be expected. At operation it is found that the length of the stenosed portion varies considerably; in cases in which the two divided ends of the aorta could not be brought together the author has anastomosed the subclavian artery to the caudal end of the divided aorta. The results of this procedure, however, have not been so good as was hoped. *H. E. Holling*

**The Blind Spot in Hypertension.** B. G. TOVBIN. *Klin. Med., Mosk.*, **26**, No. 9, 39–43, 1948.

The study of the blind spot is considered to yield useful results in the diagnosis of early hypertension. The author examined by campimetry 69 eyes in 35 patients with early hypertension. Some control studies were carried out on normal eyes. In 67 of the 69 eyes there were definite deviations from the normal which fell into two groups: (1) significant increase in the extent of the blind spot; (2) irregularities in its contours, prolongations taking the shape of knobs, teeth, and attenuated branches. Ophthalmoscopic examination revealed some changes in the fundus in 28 cases. *S. S. B. Gilder*

**Ecchymosis of the Abdominal Wall as an Early Diagnostic Sign of Dissecting Aneurysm of the Aorta.** R. GREEN and O. SAPHIR. *Amer. J. med. Sci.*, **216**, 24–26, July, 1948.

In a patient in whom the findings indicated acute embolic occlusion of the iliac artery, the presence of ecchymosis of the abdominal wall suggested the diagnosis of acute dissecting aneurysm of the aorta. This was confirmed at necropsy, the ecchymosis resulting from involvement of the deep inferior epigastric arteries. *T. Semple*

**Place of Intermittent Venous Hyperemia in the Treatment of Obliterative Vascular Disease.** M. H. EVOY and G. DE TAKATS. *Arch. intern. Med.*, **81**, 292–300, March, 1948.

Intermittent venous hyperæmia is indicated after acute arterial occlusion if embolectomy or sympathectomy is not feasible or after either procedure as post-operative treatment, and in patients with chronic arterial occlusion due to arteriosclerosis with and without diabetes, to syphilis, or to thrombo-angiitis obliterans. Patients with marked vasospasm, as in the earlier stages of thrombo-angiitis, are subjected by the authors to sympathectomy before the treatment is begun. The procedure is contraindicated in acute venous thrombosis, lymphangitis, severe arteriolar obstruction, and in the presence of frank gangrene. The treatment has been found useless for neuropathies, whether ischæmic or metabolic, causalgic states, and sequelæ of frost-bite and immersion foot.

A hundred ambulatory patients with intermittent claudication and numbness and tingling of the toes, often associated with angina pectoris, were studied over a period of one year or more, the apparatus being used at home; 35 showed notable improvement with the treatment and 32 slight improvement. Improvement was measured by noting walking ability and venous filling times. The rationale of the treatment is doubtful, but in addition to a small reactive hyperæmia a mechanical filling and stretching of the terminal vascular bed takes place during the procedure. *T. Semple*

**Dicumarol Therapy in Acute Coronary Occlusion with Myocardial Infarction.** M. MCCALL. *Amer. J. med. Sci.*, **215**, 612–616, June, 1948.

From a study at the Beekman Downtown Hospital, New York, of 71 patients with proven coronary thrombosis the conclusion was reached that dicoumarol is a therapeutic agent of safety and value; it appears to be a preventive of thromboembolic phenomena in cases of acute coronary occlusion associated with myocardial infarction. Prothrombin estimations are essential for safe therapy, but if, in spite of these, hæmorrhagic complications such as hæmaturia occur, they will respond to intravenous administration of 60 mg. of menadione. The dosage of dicoumarol is 300 mg. on the first day, with 200 mg., or less according to the prothrombin readings, daily for three or four weeks. *G. F. Walker*

**The Role of Thebesian Drainage in the Dynamics of Coronary Flow in Cases with and without Coronary Sclerosis.** P. I. HALONEN and A. AHO. *Acta path. microbiol. scand.*, **25**, 567–572, 1948.

Calf hearts and human hearts were perfused with saline and the amount of fluid reaching the various chambers was measured. It was found that drainage into the right heart by way of the venæ Thebesii was quite considerable, and this fact thus lends support to the hypothesis that a reversal of blood flow in these veins may transform them into auxiliaries to the coronary arteries whenever these are narrowed or occluded. No difference in Thebesian drainage was observed between normal hearts and those showing coronary sclerosis. *R. Salm*

**Treatment of Angina Pectoris by Infiltration of Procaine Solution Around the Superior Cervical Ganglion.** K. A. DRYAGIN. *Klin. Med., Mosk.*, **26**, No. 5, 23–26, May, 1948.

Infiltration of 30 ml. of 0·25% procaine solution into the neighbourhood of the superior cervical ganglion gave unexpectedly good results in 24 cases of angina pectoris; in 19 the attack was arrested at once and in 3 pain was greatly relieved. After 1 year, 8 out of 12 of these patients were still free from pain. A second infiltration in cases of relapse was less effective. No complications were observed. *S. S. B. Gilder*

**Angiocardiography in the Diagnosis of Congenital Heart Disease.** K. D. KEELE. *Brit. J. Radiol.*, **21**, 380–393, Aug., 1948.

The author briefly reviews the history of angiocardiography, and describes the technique employed upon a number of children. The patient was anæsthetized with cyclopropane and oxygen. It was found that the best visualization was given by films taken in the left oblique position and in the supine antero-posterior position. There were no untoward reactions. The normal appearances are described and well illustrated by line drawings. The author emphasizes that the cadaver appearance of the interior of the heart chambers is modified by the tendency to formation of an axial stream, by the presence of blood currents, and by dilution of the contrast medium.

He describes 5 cases of congenital heart lesion. These included 3 cases of patent ductus arteriosus, 1 accompanied by complete heart block, 1 by pulmonary stenosis, and 1 by a patent interauricular septum. In one of these cases the communicating channel between pulmonary artery and aorta was visualized directly. A case of coarctation of the aorta is well illustrated and the defect in the interventricular septum in a fifth case is clearly shown.

In the author's view, when a lesion is present for which, on clinical grounds, surgery is the treatment of choice, angiocardiography is indicated, both for accurate diagnosis and to reveal any co-existing abnormalities. *A. M. Rackow*

**Regulation of the Circulation in Malnutrition.** H. REINDELL and H. KLEPZIG. *Z. ges. inn. Med.*, **3**, 193–199, April, 1948.

Undernourished men and women of all ages generally have a lowered systolic and diastolic blood pressure and a slowed heart rate. The hypotension and bradycardia, which appear before any gross intestinal disturbance (such as hunger œdema), are not the result of myocardial damage or of a disturbed circulatory control. They are rather the expression of a special type of control for the sake of circulatory economy, and are associated with a diminished minute volume, a lessening of the elastic resistance, and an increase of the peripheral resistance.

*R. T. Grant*

**Circulatory Responses to Spinal and Caudal Anesthesia in Hypertension: Relation to the Effect of Sympathectomy. I. Effect on Arterial Pressure.** R. D. TAYLOR, R. BIRCHALL, A. C. CORCORAN, and I. H. PAGE. *Amer. Heart J.*, **36**, 221–225, Aug., 1948.

Observations on 43 patients before and after operation lead to the conclusion that the blood-pressure response to spinal and caudal analgesia has no more than a negative value in the selection of patients for sympathectomy.

*R. T. Grant*

**Circulatory Responses to Spinal and Caudal Anesthesia in Hypertension: Relation to the Effect of Sympathectomy. II. Effect on Renal Function.** A. C. CORCORAN, R. D. TAYLOR, and I. H. PAGE. *Amer. Heart J.*, **36**, 226–240, Aug., 1948.

High spinal or caudal analgesia, which materially reduces blood pressure in hypertensive patients, usually causes renal vasodilatation, resulting in increased renal blood flow and a slight decrease in glomerular filtration rate. This is inconsistent with the view that essential hypertension is a compensation for increased renal vascular resistance. The renal vascular response to analgesia is not a positive guide to the selection of patients for sympathectomy.

*R. T. Grant*

**A Comparative Evaluation of Tetraethylammonium Chloride and Sodium Amytal in Patients with Hypertensive Cardiovascular Disease.** I. G. TAMAGNA and C. A. POINDEXTER. *Amer. J. med. Sci.*, **215**, 651–654, June, 1948.

The effects on systolic and diastolic blood pressure of intravenous injection of tetræthyl-ammonium chloride and the standard sodium amytal test were compared in 68 hypertensive subjects. Injections of 2 ml. (0·2 mg.) of tetræthyl-ammonium chloride were given intravenously over a period of 1 to 1½ minutes, and the blood pressure was recorded until the initial level was regained. The lowest level was reached 1 to 3 minutes after the injection, and a smaller secondary fall was usual about 10 minutes after the injection. There is a parallel fall in systolic and diastolic pressures. In a comparison of the fall in the diastolic pressure in the two tests, it was found that the difference was less than 15 mm. in 51 cases, 15 to 30 mm. in 13 cases, and above 30 mm. in 4 cases. The largest discrepancies occurred in cases of malignant hypertension, the fall usually being greater with tetræthyl-ammonium chloride. Reactions were not important, but were most noticeable in patients with malignant hypertension.

The authors regard the test as an advance on the sodium amytal test in the assessment of cases for sympathectomy in view of its greater convenience and on the theoretical grounds that tetræthyl-ammonium chloride acts by blocking impulses at the sympathetic ganglia.

*J. W. Litchfield*

**Observations on Micro-nodular Pulmonary Radiological Shadows. Pulmonary Arterial Hypertension.** C. LAUBRY, J. LENÈGRE, and L. ABBAS. *Bull. Soc. méd. Hôp. Paris*, **64**, 741–749, June, 1948.

Fine nodular shadows disseminated throughout the lung-fields in association with mitral stenosis are occasionally seen on radiological examination, and have been described in Britain by Anglin, Elkeles, and Gumpert. Five further cases are here described and discussed and the literature reviewed. The small hard shadows are characteristically most densely aggregated in the mid-zones and there is a generalized fibre-mesh appearance of the lung with marked hilar congestion. The condition is seen most commonly in males between the ages of 20 and 40 with mitral stenosis and frequent hæmoptyses. In one case histological examination at necropsy showed that the nodules consisted of masses of large heart-failure cells full of iron pigment, clumped together in the alveoli and their walls. There was also much extracellular pigment. It was previously thought that the nodules consisted merely of aggregations of heart-failure cells due to capillary stasis, but here the importance is stressed of repeated hæmoptyses and subsequent phagocytosis of the red blood corpuscles.

*E. G. Sita-Lumsden*